

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

839

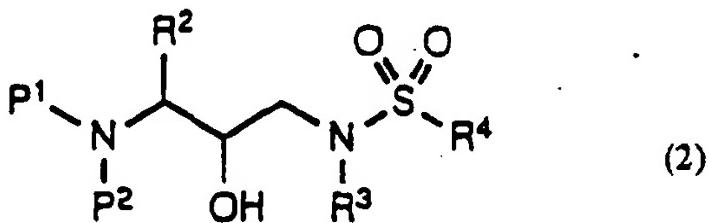
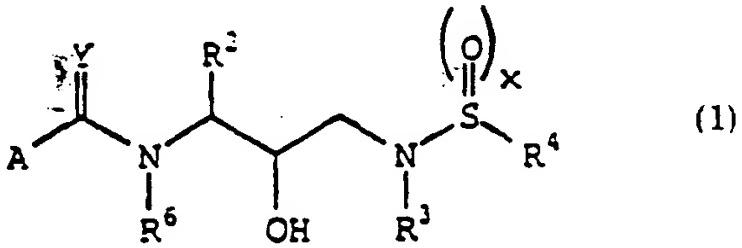
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: C07C 311/29, C07D 213/30, C07C 317/14, 311/18, C07D 387/79, C07K 5/062, A61K 31/18, 31/44	A1	(11) International Publication Number: WO 95/06030 (43) International Publication Date: 2 March 1995 (02.03.95)
(21) International Application Number: PCT/US94/09139		MUELLER, Richard, A. [US/US]; 562 Stonegate Terrace, Glencoe, IL 60022 (US). TALLEY, John, J. [US/US]; 8772 Pine Avenue, Brentwood, MO 63144 (US). GETMAN, Daniel, P. [US/US]; 66 Sunny Hill Court, Chesterfield, MO 63017 (US). DECRESCENZO, Gary, A. [US/US]; 536 Schrader Farm Drive, St. Peters, MO 63376 (US). FRESKOS, John, N. [US/US]; 7572 York, Clayton, MO 63105 (US). BERTENSHAW, Deborah, E. [US/US]; 8758 Pine Avenue, Brentwood, MO 63144 (US). HEINTZ, Robert, M. [US/US]; 603 Nancy Place, Ballwin, MO 63021 (US).
(22) International Filing Date: 23 August 1994 (23.08.94)		
(30) Priority Data: 08/110,911 24 August 1993 (24.08.93) US 08/204,827 2 March 1994 (02.03.94) US		
(60) Parent Applications or Grants (63) Related by Continuation US 08/110,911 (CON) Filed on 24 August 1993 (24.08.93) US 08/204,827 (CON) Filed on 2 March 1994 (02.03.94)		(74) Agents: UNGEMACH, Frank, S. et al.; G.D. Searie & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).
(71) Applicants (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). THE MONSANTO COMPANY [US/US]; 800 North Lindbergh Boulevard, St. Louis, MO 63167 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).
(72) Inventors; and (75) Inventors/Applicants (for US only): VAZQUEZ, Michael, L. [US/US]; 233 Saratoga Court, Gurnee, IL 60031 (US).		Published With international search report.

(54) Title: HYDROXYETHYLAMINO SULPHONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

(57) Abstract

Hydroxyethylamino sulphonamide compounds of formulae (1) and (2), wherein A, R², R³, R⁴, R⁶, x, P¹ and P² are as defined in claims 1 and 8 are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Larvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Hydroxyethylamino sulphonamides useful as retroviral protease inhibitors**RELATED APPLICATION**

5 This application is a continuation in part application of co-owned and co-pending U.S. patent application Serial No. 08/204,827 filed March 2, 1994, which is a continuation in part application of co-owned and co-pending PCT/US93/07814, filed August 24, 1993, 10 which is a continuation in part application of co-owned U.S. patent application Serial No. 07/934,984 filed August 25, 1992, now abandoned, each of which is incorporated herein by reference in its entirety.

15 **BACKGROUND OF THE INVENTION**

1. Field of the Invention

The present invention relates to retroviral protease inhibitors and, more particularly, relates to 20 novel compounds and a composition and method for inhibiting retroviral proteases. This invention, in particular, relates to sulfonamide-containing hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral 25 proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

30

2. Related Art

During the replication cycle of retroviruses, gag and gag-pol gene transcription products are translated as proteins. These proteins are subsequently processed by 35 a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into

the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious viroids. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor protein. It has also been shown through site-directed mutagenesis of an aspartic acid residue in the HIV protease active site that processing of the gag precursor protein is prevented. Thus, attempts have been made to inhibit viral replication by inhibiting the action of retroviral proteases.

15

Retroviral protease inhibition typically involves a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds (typically in a reversible manner) to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit specific processing of structural proteins and the release of retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

25

Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such compounds include hydroxyethylamine isosteres and reduced amide isosteres. See, for example, EP 0 346 847; EP 0 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors," *Science*, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8 Å Crystal Structure of a C₂ Symmetric Inhibitor Complexed to HIV-1 Protease," *Science*, 249, 527 (1990).

Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR 5 H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. EP 468 641 discloses renin inhibitors and intermediates for the preparation of the inhibitors, which include sulfonamide-10 containing hydroxyethylamine compounds, such as 3-(t-butoxycarbonyl)amino-cyclohexyl-1-(phenylsulfonyl)amino-2(5)-butanol. G.B. 2,200,115 also discloses sulfamoyl-containing hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfonamide-containing 15 hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

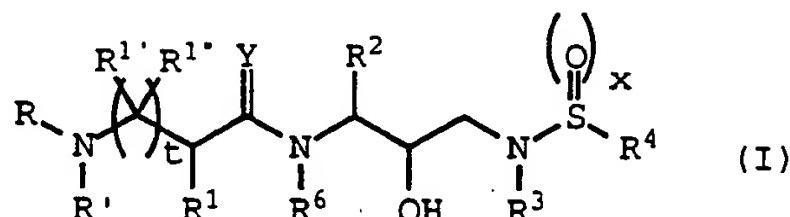
20

BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to virus 25 inhibiting compounds and compositions. More particularly, the present invention is directed to retroviral protease inhibiting compounds and compositions, to a method of inhibiting retroviral proteases, to processes for preparing the compounds and 30 to intermediates useful in such processes. The subject compounds are characterized as sulfonamide-containing hydroxyethylamine inhibitor compounds.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there
is provided a retroviral protease inhibiting compound of
5 the formula:



or a pharmaceutically acceptable salt, prodrug or ester
10 thereof, wherein:

R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl,
alkyl carbonyl, cycloalkyl carbonyl,
cycloalkyl alkoxy carbonyl, cycloalkyl alkanyl, alkanoyl,
15 aralkanyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxyalkanyl, heterocyclic carbonyl,
heterocyclicloxy carbonyl, heterocyclic alkanyl,
heterocyclic alkoxy carbonyl, heteroaralkanyl,
heteroaralkoxy carbonyl, heteroaryloxy carbonyl,
20 heteroaroyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,
aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl,
aminocarbonyl, aminoalkanyl, and mono- and disubstituted
aminocarbonyl and mono- and disubstituted aminoalkanyl
radicals wherein the substituents are selected from
25 alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
heteroaryl, heteroaralkyl, heterocycloalkyl,
heterocycloalkyl radicals, or where said
aminocarbonyl and aminoalkanyl radicals are
disubstituted, said substituents along with the nitrogen
30 atom to which they are attached form a heterocycloalkyl
or heteroaryl radical;

R' represents hydrogen, radicals as defined for R³ or
RⁿSO₂⁻ wherein Rⁿ represents radicals as defined for R³;

or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals;

5 R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyano alanine and 15 valine side chains;

R^{1'} and R^{1''} independently represent hydrogen and radicals as defined for R¹, or one of R^{1'} and R^{1''}, together with R¹ and the carbon atoms to which R¹, R^{1'} and R^{1''} are attached, represent a cycloalkyl radical;

20 R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen 25 radials, -NO₂, -CN, -CF₃, -OR⁹ and -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals, and halogen radicals;

30 R³ represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from 35 alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a

disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

5 R⁴ represents radicals as defined by R³ except for hydrogen;

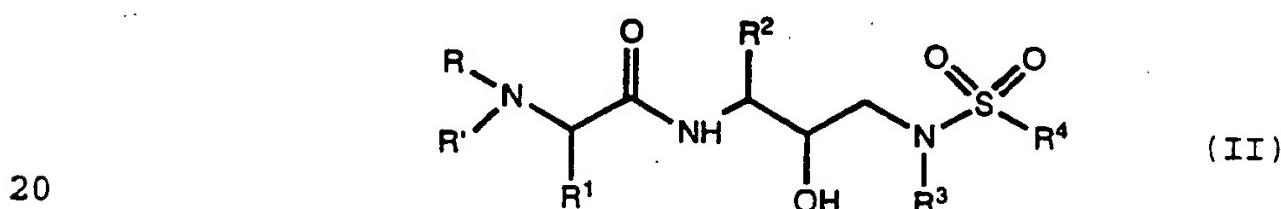
R⁶ represents hydrogen and alkyl radicals;

10 x represents 0, 1 or 2;

t represents either 0 or 1; and

Y represents O, S and NR¹⁵ wherein R¹⁵ represents
15 hydrogen and radicals as defined for R³.

A family of compounds of particular interest within Formula I are compounds embraced by Formula II:



wherein:

25 R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl,
alkyl carbonyl, cycloalkyl carbonyl,
cycloalkyl alkoxy carbonyl, cycloalkyl alkanoyl, alkanoyl,
aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
aryloxy alkanoyl, heterocyclic carbonyl,
heterocyclic alkoxy carbonyl, heterocyclic alkanoyl,
30 heterocyclic alkoxy carbonyl, heteroaralkanoyl,
heteroaralkoxy carbonyl, heteroaryloxy carbonyl,
heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
aryloxy alkyl, heteroaryloxy alkyl, hydroxy alkyl,
aminocarbonyl, amino alkanoyl, and mono- and disubstituted

- aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl,
- 5 heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;
- 10 R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;
- 15 R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine
- 20 and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, O-methyl serine, aspartic acid, beta-cyano alanine and
- 25 valine side chains;
- R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen
- 30 radials, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals;
- R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
- 35 heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said

substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said
5 substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R⁴ represents radicals as defined by R³.

10

A more preferred family of compounds within Formula II consists of compounds wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,
15 alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted
20 aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said
25 aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R³ or
35 R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

- R¹ represents CH₂C(O)NHCH₃, C(CH₃)₂(SCH₃), C(CH₃)₂(S[O]CH₃), C(CH₃)₂(S[O]₂CH₃), alkyl, alkenyl and alkynyl radicals, and amino acid side chains selected
5 from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;
- 10 R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents alkyl radicals; and
- 15 R³ and R⁴ independently represent alkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.
- 20 Of highest interest are compounds within Formula II wherein
- R represents alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl,
25 cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclloxycarbonyl, heterocyclalkoxycarbonyl, heteroaralkanoyl,
30 heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl,
35 cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said

substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

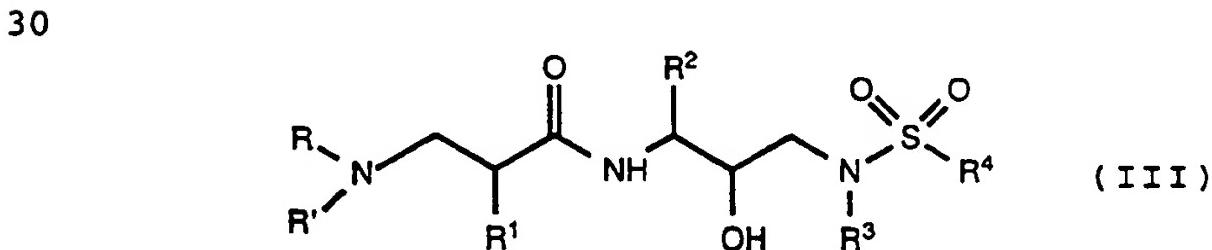
- 5 R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;
- 10 R¹ represents CH₂C(O)NHCH₃, C(CH₃)₂(SCH₃), C(CH₃)₂(S[O]CH₃), C(CH₃)₂(S[O]₂CH₃), methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, 15 iso-leucine, and beta-cyano alanine side chains;

R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

- 20 R³ represents isoamyl, n-butyl, isobutyl and cyclohexyl radicals; and

- 25 R⁴ represents phenyl, substituted phenyl and methyl radicals.

Another family of compounds of particular interest within Formula I are compounds embraced by Formula III:



wherein:

- 35 R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl,

cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclloxycarbonyl, heterocyclalkanoyl,

5 heterocyclalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted

10 aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or where said

15 aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R³ or

20 R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃,

25 -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO₂) derivatives

30 thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;

35 R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally

substituted with a group selected from alkyl and halogen radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹ represents hydrogen and alkyl;

- 5 R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said
10 substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they
15 are attached, form a heterocycloalkyl or a heteroaryl radical; and

R⁴ represents radicals as defined by R³.

- 20 A more preferred family of compounds within Formula III consists of compounds wherein

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl,
25 cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclloxycarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heteroaralkanoyl,
30 heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl
35 radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl,

heterocycloalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

5

R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

10

R¹ represents hydrogen, alkyl and alkenyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and 15 allo-isoleucine;

R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with 20 halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl and halogen radicals; and

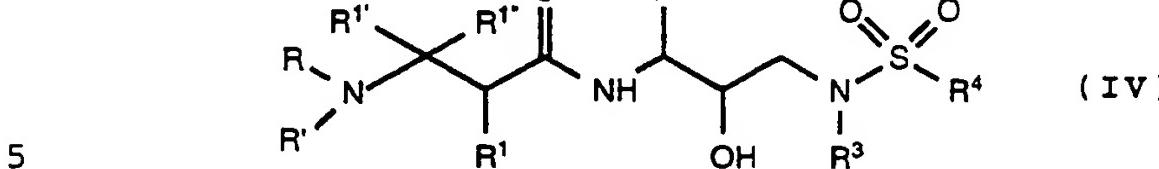
R³ and R⁴ independently represent alkyl, alkenyl, 25 alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals.

Of highest interest are compounds within 30 Formula III wherein

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, 35 aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclloxycarbonyl, heterocyclalkanoyl.

- heterocyclalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and
disubstituted aminocarbonyl and mono- and disubstituted
5 aminoalkanoyl radicals wherein the substituents are
selected from alkyl, aryl, aralkyl, cycloalkyl,
cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, heterocycloalkyalkyl radicals, or where
said aminoalkanoyl radical is disubstituted, said
10 substituents along with the nitrogen atom to which they
are attached form a heterocycloalkyl or heteroaryl
radical;
- R' represents hydrogen and radicals as defined for R³ or
15 R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;
- R¹ represents hydrogen, methyl, propargyl, t-butyl,
20 isopropyl and sec-butyl radicals, and amino acid side
chains selected from the group consisting of asparagine,
valine, S-methyl cysteine, allo-iso-leucine, iso-leucine,
threonine, serine, aspartic acid, beta-cyano alanine, and
allo-threonine side chains;
- 25 R² represents CH₃SCH₂CH₂- , iso-butyl, n-butyl, benzyl,
4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl
radicals; and
- 30 R³ represents alkyl, cyclohexyl, isobutyl, isoamyl, and
n-butyl radicals; and
- R⁴ represents methyl, phenyl and substituted phenyl
radicals wherein the substituents are selected from halo,
35 alkoxy, hydroxy, nitro and amino substituents.

Another family of compounds of particular interest within Formula I are compounds embraced by Formula IV:



5

wherein:

- R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl,
- 10 cycloalkyl alkoxy carbonyl, cycloalkyl alkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxy alkanoyl, heterocyclic carbonyl, heterocyclic oxycarbonyl, heterocyclic alkoxy carbonyl, heteroaralkanoyl,
- 15 heteroaralkoxy carbonyl, heteroaryloxy carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxy alkyl, heteroaryloxy alkyl, hydroxy alkyl, aminocarbonyl, amino alkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted amino alkanoyl
- 20 radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkyl alkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or where said amino alkanoyl radical is disubstituted, said substituents
- 25 along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

- R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

- R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃),
- 35 -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl,

- alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine,
5 tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;
- 10 R^1' and R^1'' independently represent hydrogen and radicals as defined for R^1 , or one of R^1' and R^1'' , together with R^1 and the carbon atoms to which R^1 , R^1' and R^1'' are attached, represent a cycloalkyl radical;
- 15 R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-\text{NO}_2$, $-\text{C}\equiv\text{N}$, CF_3 , $-\text{OR}^9$ and $-\text{SR}^9$, wherein R^9 represents hydrogen and alkyl radicals;
20
 R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and
25 disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said
30 substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and
- 35 R^4 represents radicals as defined by R^3 .

A more preferred family of compounds within Formula IV consists of compounds wherein

- R represents an arylalkanoyl, heteroaroyl,
aryloxyalkanoyl, aryloxycarbonyl, alkanoyl,
aminocarbonyl, mono-substituted aminoalkanoyl, or
5 disubstituted aminoalkanoyl, or mono-or
dialkylaminocarbonyl radical;
- R' represents hydrogen and radicals as defined for R³ or
R and R' together with the nitrogen to which they are
10 attached represent a heterocycloalkyl or heteroaryl
radical;
- R¹, R^{1'} and R^{1''} independently represent hydrogen and
alkyl radicals having from 1 to about 4 carbon atoms,
15 alkenyl, alkynyl, aralkyl radicals, and radicals
represented by the formula -CH₂C(O)R" or -C(O)R" wherein
R" represents R³⁸, -NR³⁸R³⁹ and OR³⁸ wherein R³⁸ and R³⁹
independently represent hydrogen and alkyl radicals
having from 1 to about 4 carbon atoms;
- 20 R² represents alkyl, cycloalkylalkyl and aralkyl
radicals, which radicals are optionally substituted with
halogen radicals and radicals represented by the formula
-OR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl
25 radicals; and
- R³ and R⁴ independently represent alkyl, alkenyl,
alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl,
30 heteroaryl and heteroaralkyl radicals.

Of highest interest are compounds of Formula IV
wherein:

- 35 R represents an arylalkanoyl, aryloxycarbonyl,
aryloxyalkanoyl, alkanoyl, aminocarbonyl, mono-

substituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono- or dialkylaminocarbonyl radical;

5 R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent a heterocycloalkyl or heteroaryl radical;

10 R¹, R^{1'} and R^{1''} independently represent hydrogen, methyl, ethyl, benzyl, phenylpropyl and propargyl radicals;

R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

15 R³ represents alkyl, cyclohexyl, isobutyl, isoamyl and n-butyl radicals; and

20 R⁴ represents methyl, phenyl and substituted phenyl radicals wherein the substituents are selected from halo, alkoxy, amino and nitro substituents.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 10 carbon atoms, preferably from 1 to about 8 carbon atoms, more preferably 1-5 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to about 18 carbon atoms, preferably from 2 to about 8 carbon atoms, more preferably from 2 to about 5 carbon atoms. Examples of suitable alkenyl radicals include ethenyl, propenyl, alkyl, 1,4-butadienyl and the like. The term "alkynyl", alone or in

combination, means a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to about 10 carbon atoms, more preferably from 2 to about 5 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, (propargyl), butynyl and the like. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms, more preferably from about 3 to about 6 carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical as defined above. Examples of such cycloalkylalkyl radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylbutyl and the like. The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxy carbonyl, cycloalkyl, heterocycloalkyl, amido, mono and dialkyl substituted amino, mono and dialkyl substituted amido and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-

aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl and the like. The terms "aralkyl" and 5 "aralkoxy", alone or in combination, means an alkyl or alkoxy radical as defined above in which at least one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, benzyloxy, 2-phenylethyl, dibenzylmethyl, hydroxyphenylmethyl, methylphenylmethyl, 10 and the like. The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O-C(O)- in which the term "aralkyl" has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl and 4-methoxyphenylmethoxycarbonyl. 15 The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, 20 valeryl, 4-methylvaleryl, and the like. The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl, and the like, or from a benz-fused 25 monocyclic cycloalkanecarboxylic acid which is optionally substituted by one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxy carbonyl, cycloalkyl, heterocycloalkyl, alkanoylamino, amido, mono and dialkyl 30 substituted amino, mono and dialkyl substituted amido and the like, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 35 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the

like. The term "aroyl" means an acyl radical derived from an arylcarboxylic acid, aryl having the meaning given above. Examples of such arylcarboxylic acid radicals include substituted and unsubstituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like. The terms "heterocyclyl" and "heterocycloalkyl," alone or in combination, mean a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 12 ring members, more preferably 5 to 10 ring members and most preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen and sulphur, and which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, hydroxy, oxo, aryl, aralkyl and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by hydroxy, alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl and/or on a tertiary nitrogen atom (i.e., =N-) by oxido. Heterocycloalkyl and heterocyclyl also includes benz-fused monocyclic cycloalkyl groups having at least one such heteroatom. Heterocycloalkyl and heterocyclyl in addition to sulfur and nitrogen also includes sulfones, sulfoxides and N-oxides of tertiary nitrogen containing heterocycloalkyl groups. The term "heteroaryl", alone or in combination, means an aromatic monocyclic, bicyclic, or tricyclic heterocyclyl (heterocycloalkyl) radical as defined above and is optionally substituted as defined above with respect to the definitions of aryl and heterocyclyl (heterocycloalkyl). Examples of such heterocyclyl (heterocycloalkyl) and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl,

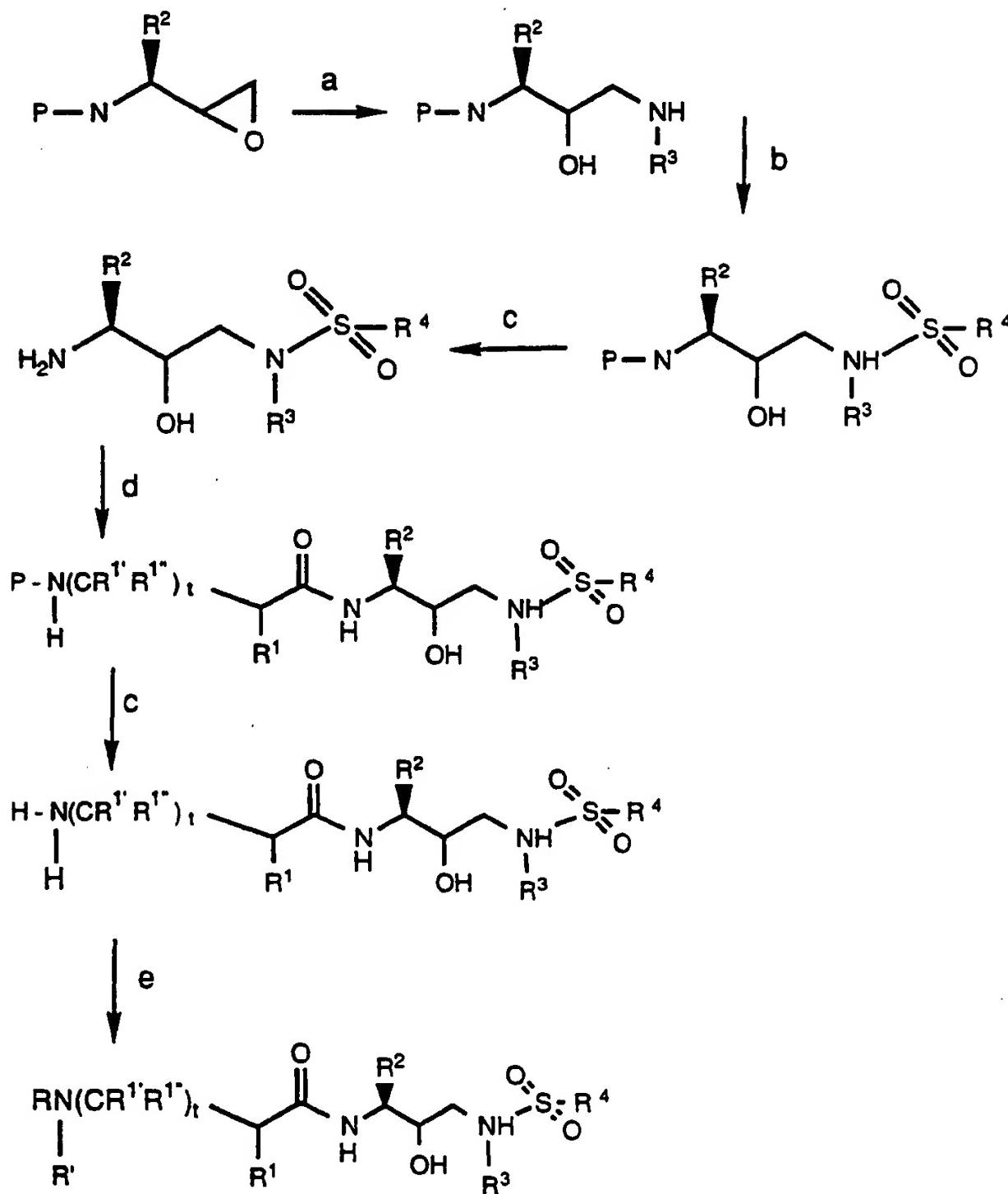
pyridyl, (e.g., 2-(1-piperidinyl)pyridyl and 2-(4-benzyl piperazin-1-yl-1-pyridinyl), pyrazinyl, pyrimidinyl, furyl, tetrahydrofuryl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, β -carbolinyl, 2-benzofurancarbonyl, 1-, 2-, 4- or 5-benzimidazolyl, and the like. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula 15 cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the meaning given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the meaning given above. The term "heterocycloalkoxycarbonyl" means an acyl group derived from heterocycl-0-COOH wherein heterocycl is as defined above. The term "heterocycloalkylalkanoyl" is an acyl radical derived from a heterocycloalkyl-substituted alkylcarboxylic acid wherein heterocycloalkyl has the meaning given above. The term 20 "heterocycloalkylalkoxycarbonyl" means an acyl radical derived from a heterocycloalkyl-substituted alkyl-O-COOH wherein heterocycloalkyl has the meaning given above. The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-0-COOH wherein heteroaryl has the meaning given above. The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, 30 aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkylcarboxylic acid 35

preparation of compounds having the specified stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R). However, such procedures are generally applicable
5 to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For example, a compound having the (R)
10 stereochemistry can be inverted to the (S) stereochemistry using well-known methods.

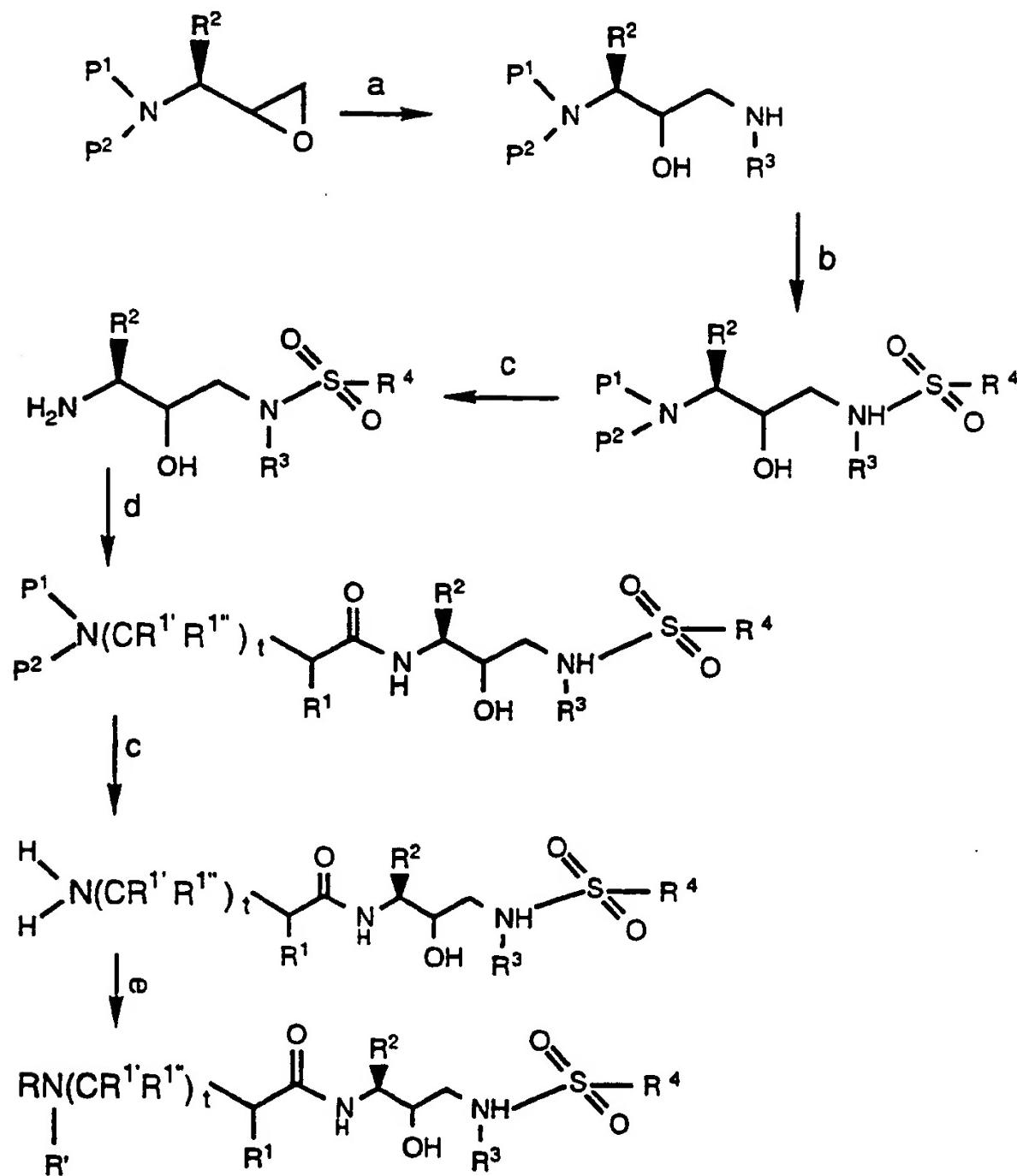
Preparation of Compounds of Formula I

15 The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedure. This procedure is schematically shown in the following Schemes I and II:

25

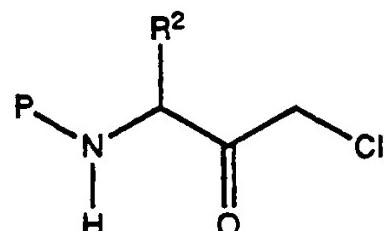
SCHEME I

- a) amine b) sulfonyl chloride R⁴SO₂Cl (or anhydride) + acid scavenger c) deprotection d) coupling e) coupling.

SCHEME II

a) amine b) sulfonyl chloride R⁴SO₂Cl (or anhydride) + acid
scavenger c) deprotection d) coupling e) coupling.

An N-protected chloroketone derivative of an amino acid having the formula:

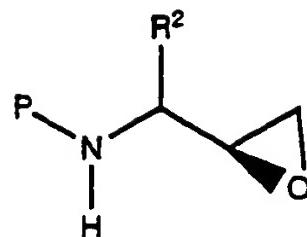


5

wherein P represents an amino protecting group, and R² is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include 10 carbobenzoxy, t-butoxycarbonyl, and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The 15 reduction reaction is conducted at a temperature of from -10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran, and the like. The N-protected chloroketones are commercially available, e.g., such as 20 from Bachem, Inc., Torrance, California. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

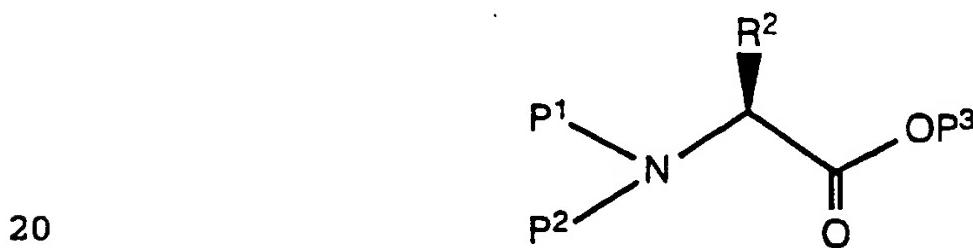
25

The halo alcohol can be utilized directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino 30 epoxide of the formula:



wherein P and R² are as defined above. Suitable solvent systems for preparing the amino epoxide include ethanol, 5 methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium t-butoxide, DBU and the like. A preferred base is 10 potassium hydroxide.

Alternatively, a protected amino epoxide can be prepared, such as in co-owned and co-pending PCT Patent Application Serial No. PCT/US93/04804 which is 15 incorporated herein by reference, starting with an L-amino acid which is reacted with a suitable amino-protecting group in a suitable solvent to produce an amino-protected L-amino acid ester of the formula:



wherein P³ represents carboxyl-protecting group, e.g., methyl, ethyl, benzyl, tertiary-butyl and the like; R² is as defined above; and P¹ and P² independently are selected 25 from amine protecting groups, including but not limited to, arylalkyl, substituted arylalkyl, cycloalkenylalkyl and substituted cycloalkenylalkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl and silyl. Examples of arylalkyl include, but are not limited to benzyl, ortho- 30 methylbenzyl, trityl and benzhydryl, which can be

optionally substituted with halogen, alkyl of C₁-C₈, alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl,

5 naphthalenyl, indanyl, anthracenyl, durenyl, 9-(9-phenylfluorenyl) and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkenylalkyl radicals containing cycloalkyls of C₆-C₁₀. Suitable acyl groups include carbobenzoxy, t-butoxycarbonyl, iso-butoxycarbonyl,

10 benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloroacetyl, phthaloyl and the like.

Additionally, the P¹ and/or P² protecting groups can form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted,

15 e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl.

Silylation of the amine functions to provide mono- or bis-disilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the aminoalcohol can lead to the N,N,O-tri-silyl derivative.

30 Removal of the silyl function from the silyl ether function is readily accomplished by treatment with, for example, a

metal hydroxide or ammonium flouride reagent, either as a discrete reaction step or in situ during the preparation of the amino aldehyde reagent. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-

5 dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethylsilyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine

10 derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

15 Preferably P¹ and P² are independently selected from aralkyl and substituted aralkyl. More preferably, each of P¹ and P² is benzyl. As illustrated in the Examples below, P, P¹ and P² may serve as a nitrogen protecting group which is later removed in the

20 preparation of compounds of this invention or may form a part of the final inhibitor structure. For example, benzoyl, benzyloxycarbonyl, t-butoxycarbonyl, pyridylmethoxycarbonyl, tetrahydrofuryloxycarbonyl, pyridylcarbonyl and the like can used to both protect a

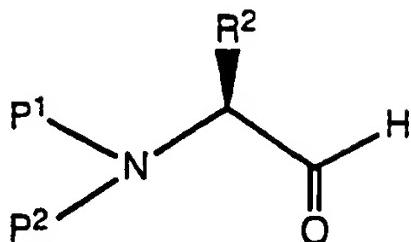
25 nitrogen from undergoing an undesired reaction and also be part of the structure of an active enzyme inhibitor.

The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the

30 amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at -78° C in a suitable solvent such as toluene. Preferred reducing agents include lithium aluminium hydride, lithium borohydride, sodium borohydride, borane, lithium tri-ter-

35 butoxyaluminum hydride, borane/THF complex. Most preferably, the reducing agent is diisobutylaluminum hydride (DiBAL-H) in toluene. The resulting alcohol is

then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



5

wherein P¹, P² and R² are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred 10 for 35 minutes.

Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chloride and DMSO, acetyl chloride or anhydride 15 and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydro thiophene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO, 20 dimethylphosphoryl chloride and DMSO and isobutyl chloroformate and DMSO. The oxidation conditions reported by Reetz et al [Angew Chem., 99, p. 1186, (1987)], [Angew Chem. Int. Ed. Engl., 26, p. 1141, 1987] employed oxalyl chloride and DMSO at -78°C.

25

The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral 30 protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need

for the use of low temperature reactor which makes the process more suitable for commercial production.

The reaction may be carried out under and

5 inert atmosphere such as nitrogen or argon, or normal or dry air, under atmospheric pressure or in a sealed reaction vessel under positive pressure. Preferred is a nitrogen atmosphere. Alternative amine bases include, for example, tri-butyl amine, tri-isopropyl

10 amine, N-methylpiperidine, N-methyl morpholine, azabicyclononane, diisopropylethylamine, 2,2,6,6-tetramethylpiperidine, N,N-dimethylaminopyridine, or mixtures of these bases. Triethylamine is a preferred base. Alternatives to pure DMSO as solvent include

15 mixtures of DMSO with non-protic or halogenated solvents such as tetrahydrofuran, ethyl acetate, toluene, xylene, dichloromethane, ethylene dichloride and the like. Dipolar aprotic co-solvents include acetonitrile, dimethylformamide, dimethylacetamide,

20 acetamide, tetramethyl urea and its cyclic analog, N-methylpyrrolidone, sulfolane and the like. Rather than N,N-dibenzylphenylalaninol as the aldehyde precursor, the phenylalaninol derivatives discussed above can be used to provide the corresponding

25 N-monosubstituted [either P¹ or P² = H] or N,N-disubstituted aldehyde.

In addition, hydride reduction of an amide or ester derivative of the corresponding alkyl, benzyl or cycloalkenyl nitrogen protected phenylalanine, substituted phenylalanine or cycloalkyl analog of phenylalanine derivative can be carried out to provide the aldehydes. Hydride transfer is an additional method of aldehyde synthesis under conditions where

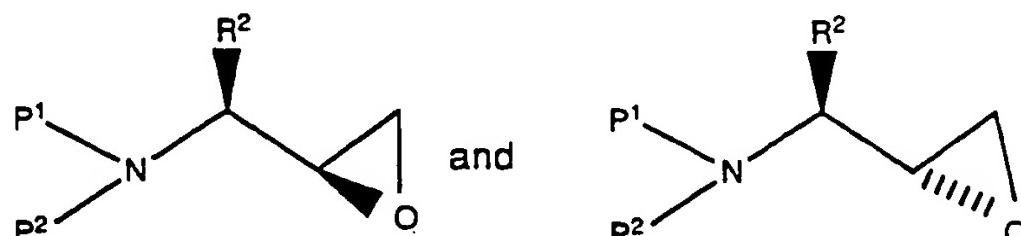
30 aldehyde condensations are avoided, cf, Oppenauer Oxidation.

The aldehydes of this process can also be prepared by methods of reducing protected phenylalanine and phenylalanine analogs or their amide or ester derivatives by, e.g., sodium amalgam with HCl in ethanol or lithium or sodium or potassium or calcium in ammonia. The reaction temperature may be from about -20°C to about 45°C, and preferably from about 5°C to about 25°C. Two additional methods of obtaining the nitrogen protected aldehyde include oxidation of the corresponding alcohol with bleach in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-pyridyloxy free radical. In a second method, oxidation of the alcohol to the aldehyde is accomplished by a catalytic amount of tetrapropylammonium perruthenate in the presence of N-methylmorpholine-N-oxide.

15

Alternatively, an acid chloride derivative of a protected phenylalanine or phenylalanine derivative as disclosed above can be reduced with hydrogen and a catalyst such as Pd on barium carbonate or barium sulphate, with or without an additional catalyst moderating agent such as sulfur or a thiol (Rosenmund Reduction).

The aldehyde resulting from the Swern oxidation is then reacted with a halomethylolithium reagent, which reagent is generated *in situ* by reacting an alkyllithium or aryllithium compound with a dihalomethane represented by the formula $x^1\text{CH}_2x^2$ wherein x^1 and x^2 independently represent I, Br or Cl. For example, a solution of the aldehyde and chloroiodomethane in THF is cooled to -78° C and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:



The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be 5 separated. For compounds having the (S) stereochemistry, a D-amino acid can be utilized in place of the L-amino acid.

The addition of chloromethyl lithium or 10 bromomethyl lithium to a chiral amino aldehyde is highly diastereoselective. Preferably, the chloromethyl lithium or bromomethyl lithium is generated in-situ from the reaction of the dihalomethane and n-butyllithium. Acceptable methyleneating halomethanes include chloroiodomethane, 15 bromochloromethane, dibromomethane, diiodomethane, bromofluoromethane and the like. The sulfonate ester of the addition product of, for example, hydrogen bromide to formaldehyde is also a methyleneating agent.

Tetrahydrofuran is the preferred solvent, however 20 alternative solvents such as toluene, dimethoxyethane, ethylene dichloride, methylene chloride can be used as pure solvents or as a mixture. Dipolar aprotic solvents such as acetonitrile, DMF, N-methylpyrrolidone are useful as solvents or as part of a solvent mixture. The reaction can 25 be carried out under an inert atmosphere such as nitrogen or argon. For n-butyl lithium can be substituted other organometallic reagents such as methyl lithium, tert-butyl lithium, sec-butyl lithium, phenyllithium, phenyl sodium and the like. The reaction can be carried out at 30 temperatures of between about -80°C to 0°C but preferably between about -80°C to -20°C. The most preferred reaction temperatures are between -40°C to -15°C. Reagents can be added singly but multiple additions are preferred in certain conditions. The preferred pressure of the reaction is 35 atmospheric however a positive pressure is valuable under certain conditions such as a high humidity environment.

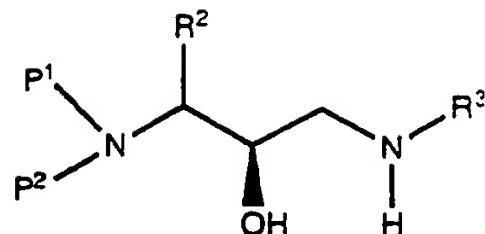
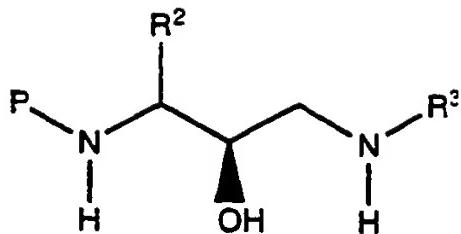
Alternative methods of conversion to the epoxides of this invention include substitution of other charged methylenation precursor species followed by their treatment with base to form the analogous anion. Examples of these 5 species include trimethylsulfoxonium tosylate or triflate, tetramethylammonium halide, methyldiphenylsulfoxonium halide wherein halide is chloride, bromide or iodide.

The conversion of the aldehydes of this invention 10 into their epoxide derivative can also be carried out in multiple steps. For example, the addition of the anion of thioanisole prepared from, for example, a butyl or aryl lithium reagent, to the protected aminoaldehyde, oxidation of the resulting protected aminosulfide alcohol with well 15 known oxidizing agents such as hydrogen peroxide, tert-butyl hypochlorite, bleach or sodium periodate to give a sulfoxide. Alkylation of the sulfoxide with, for example, methyl iodide or bromide, methyl tosylate, methyl mesylate, methyl triflate, ethyl bromide, isopropyl bromide, benzyl 20 chloride or the like, in the presence of an organic or inorganic base Alternatively, the protected aminosulfide alcohol can be alkylated with, for example, the alkylating agents above, to provide a sulfonium salts that are subsequently converted into the subject epoxides with tert- 25 amine or mineral bases.

The desired epoxides formed, using most preferred conditions, diastereoselectively in ratio amounts of at least about an 85:15 ratio (S:R). The product can be 30 purified by chromatography to give the diastereomerically and enantiomerically pure product but it is more conveniently used directly without purification to prepare retroviral protease inhibitors. The foregoing process is applicable to mixtures of optical isomers as well as 35 resolved compounds. If a particular optical isomer is desired, it can be selected by the choice of starting material, e.g., L-phenylalanine, D-phenylalanine, L-

phenylalaninol, D-phenylalaninol, D-hexahydrophenylalaninol and the like, or resolution can occur at intermediate or final steps. Chiral auxiliaries such as one or two equivalents of camphor sulfonic acid, citric acid, camphoric acid, 2-methoxyphenylacetic acid and the like can be used to form salts, esters or amides of the compounds of this invention. These compounds or derivatives can be crystallized or separated chromatographically using either a chiral or achiral column as is well known to those skilled 10 in the art.

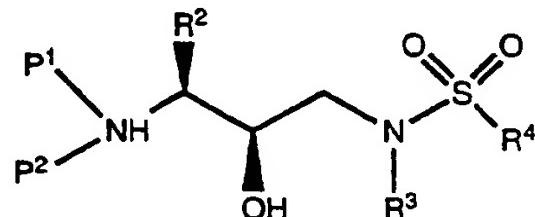
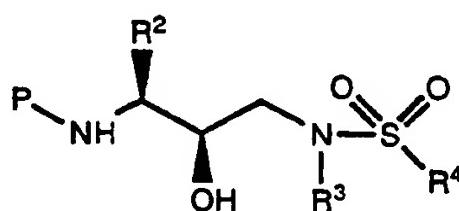
The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess of, a desired amine of the formula 15 R^3NH_2 , wherein R^3 is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. 20 Suitable solvent systems include protic, non-protic and dipolar aprotic organic solvents such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, isopropanol, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, 25 N,N -dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. Exemplary amines corresponding to the formula R^3NH_2 include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, naphthylene methyl 30 amine and the like. The resulting product is a 3-(N -protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) can be represented by the formulas:



wherein P, P¹, P², R² and R³ are as described above.

Alternatively, a haloalcohol can be utilized in place of
5 the amino epoxide.

The amino alcohol defined above is then reacted in a suitable solvent with a sulfonyl chloride (R⁴SO₂Cl) or sulfonyl anhydride in the presence of an acid 10 scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride, tetrahydrofuran. Suitable acid scavengers include triethylamine, pyridine. Preferred sulfonyl chlorides are methanesulfonyl chloride and benzenesulfonyl chloride. The resulting sulfonamide derivative can be represented, depending on the epoxide utilized by the formulas
15



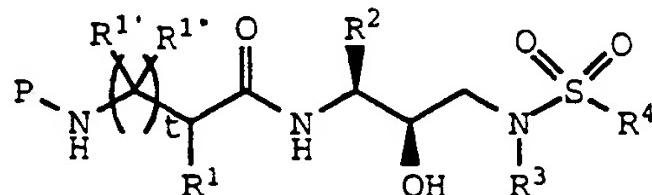
20 wherein P, P¹, P², R², R³ and R⁴ are as defined above. These intermediates are useful for preparing inhibitor compounds of the present invention and are also active inhibitors of retroviral proteases.

25 The sulfonyl halides of the formula R⁴SO₂X can be prepared by the reaction of a suitable Grignard or alkyl lithium reagent with sulfonyl chloride, or sulfur dioxide followed by oxidation with a halogen, preferably chlorine. Also, thiols may be oxidized to sulfonyl
30 chlorides using chlorine in the presence of water under carefully controlled conditions. Additionally, sulfonic

acids may be converted to sulfonyl halides using reagents such as PC15, and also to anhydrides using suitable dehydrating reagents. The sulfonic acids may in turn be prepared using procedures well known in the art. Such sulfonic acids are also commercially available. In place of the sulfonyl halides, sulfinyl halides (R^4SOX) or sulfenyl halides (R^4SX) can be utilized to prepare compounds wherein the $-SO_2-$ moiety is replaced by an $-SO-$ or $-S-$ moiety, respectively.

10

Following preparation of the sulfonamide derivative, the amino protecting group P or P^1 and P^2 amino protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g., HCl or trifluoroacetic acid, in a suitable solvent system, e.g., dioxane or methylene chloride. The resulting product is the amine salt derivative. Following neutralization of the salt, the amine is then reacted with an amino acid or corresponding derivative thereof represented by the formula $(PN[CR^{1'} R^{1''}]_t CH(R^1)COOH)$ wherein t, R^1 , $R^{1'}$ and $R^{1''}$ are as defined above, to produce the antiviral compounds of the present invention having the formula:



wherein t, P, R₁, R_{1'}, R_{1''}, R₂, R₃ and R₄ are as defined above. Preferred protecting groups in this instance are a benzyloxycarbonyl group or a t-butoxycarbonyl group. Where t is 0 and R₁ is alkyl, alkenyl, alkynyl,

5 cycloalkyl, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂[S(O)CH₃], -C(CH₃)₂[S(O₂)CH₃], or an amino acid side chain, such materials are well known and many are commercially available from Sigma-Aldrich.

10

Where the amine is reacted with a derivative of an amino acid, e.g., when t=1, so that the amino acid is a β-amino acid, such β-amino acids can be prepared according to the procedure set forth in a co-owned, 15 copending patent application, U.S. Serial No. 07/853,561 or the following procedures.

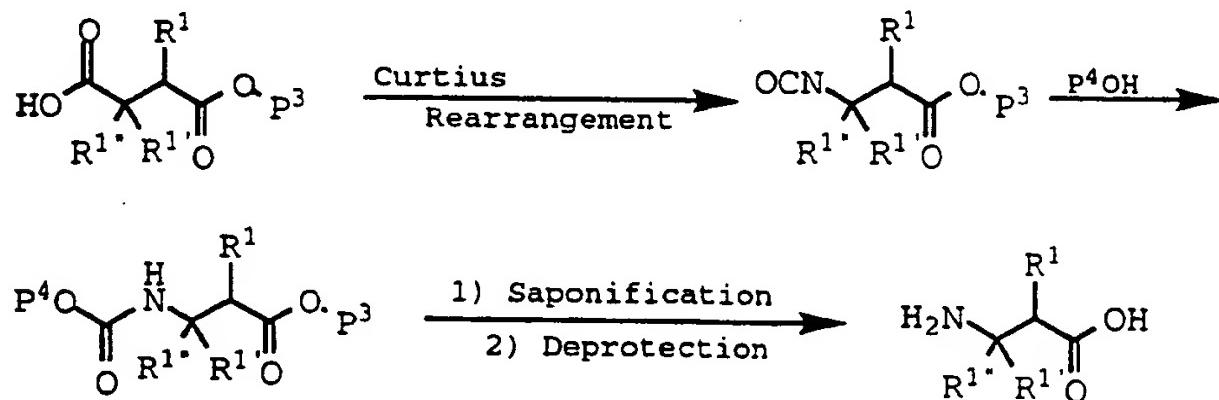
Various methods have been proposed for the preparation of chiral β-amino acids. See, for example, 20 Chemistry and Biochemistry of Amino Acids, Vol. 4, Chapter 5, pp. 250-57, B. Weinstein, Ed., Dekker, N.Y. (1975). Furukawa et al, Chem. Pharm. Bull., 25, 1319 (1977), disclose asymmetric synthesis of β-amino acids by addition of chiral amines to carbon-carbon double bonds 25 having nitrile or ester groups in the α-position. However, optical purities of the β-amino acids thus produced range from 2 to 19%. Furukawa et al also report that optically active β-amino acids have been produced with optical purities ranging from 2 to 28% by reacting 30 chiral Schiff bases with Reformsky reagent. Terentev et al, Dohl. Ahad. Nauk SSR, 163,674 (1965) disclose synthesis of β-aminobutyric acids involving addition of chiral amines to crotonic acid with optical purities ranging from 7-9%.

35

Brown et al, Tetrahedron Lett., Vol. 28, No. 19, pp 2179-2182 (1987), disclose a method of preparing

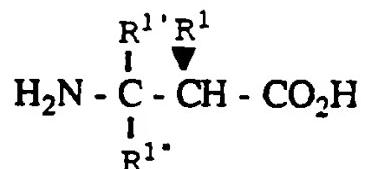
optically active disubstituted β -amino acids which involves asymmetric catalytic hydrogenation of N-substituted α -(aminoalkyl) acrylates. In order to verify the stereochemistry of the product, Curtius rearrangement was effected on the monomethyl ester of optically enriched RR-anti-2,3-dimethyl-succinic acid and trapping of the incipient isocyanate derivative with tertiary alcohol, namely, t-butyl alcohol, to give the corresponding R-enriched β -amino acid. Ninomita et al., Tetrahedron Lett., Vol. 30, 2152-2157 (1975) studied the Curtius rearrangement utilizing benzoic acid, diphenylphosphoryl azide and triethylamine followed by treatment with various alcohols and found that t-butyl alcohol gives yields superior to benzyl alcohol, ethanol and phenol.

Utilization of a primary or secondary alcohol to trap an isocyanate derivative of a chiral mono-substituted succinate, and, in particular, in a Curtius rearrangement of a chiral mono-substituted succinate, to produce chiral β -amino acids significantly increases the overall yield. The resulting carbamate-protected β -amino esters are then saponified to produce the corresponding carbamate-protected β -amino acids which are then deprotected to produce β -amino acids possessing the same absolute configuration as naturally-occurring (L)-amino acids. The overall reaction sequence can be shown as follow:

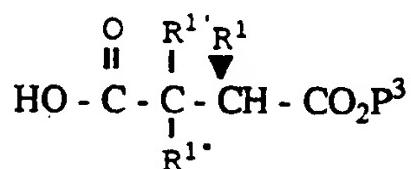


wherein R¹, R^{1'}, R^{1''}, and P³ are as defined above and P⁴OH are preferably represents radicals derived from primary and secondary alcohols.

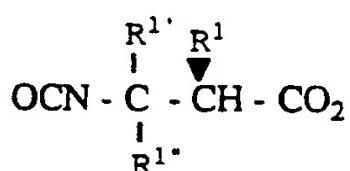
- 5 This process can also be used in the asymmetric synthesis of β-amino acids represented by the formula:



- 10 wherein R¹, R^{1'} and R^{1''} are as defined above. Such compounds are formed by Curtius rearrangement of 2(R)-substituted succinates represented by the formula



- 15 wherein R¹, R^{1'}, R^{1''} and P³ are as defined above, to afford the isocyanate derivative:



- 20 Using 2(S)-substituted succinates, 2(S)-substituted β-amino acids can also be prepared stereospecifically.

- Curtius rearrangement involves pyrolysis of acyloil azides (R-C(=O)-N=N=N) to yield isocyanates (R-N=C=O) which can be subsequently hydrolyzed to give amines. See March, Advanced Organic Chemistry, p. 1005, 2nd ed (1977). As a general rule, Curtius rearrangement is a concerted reaction and therefore proceeds with retention 30 of configuration of the starting materials.

Determination of specific reaction conditions for effecting Curtius rearrangements of various succinates is within the skill of one in the art familiar with such reactions. In the method of the present invention,

5 Curtius rearrangement to afford the desired isocyante is preferably effected by treating a 2-substituted succinate with one equivalent of diphenoxypyrophosphoryl azide $(PhO)_2PON_3$ and triethylamine to form the acyl azide followed by heating in an inert solvent, such as in warm

10 toluene, preferably at about 80°C for about three hours, to afford the isocyante derivative.

Suitable primary and secondary alcohols include those represented by the formula P^4OH where P^4 represents substituted and unsubstituted alkyl, cycloalkyl, aralkyl and aryl radicals, as well as suitable equivalents such as, for example, silyl radicals. Preferably, the primary and secondary alcohols are those wherein P^4 represents substituted and unsubstituted, straight chain as well as branched chain, alkyl radicals having from 1 to about 12 carbon atoms, substituted and unsubstituted cycloalkyl radicals having from 4 to about 7 carbon atoms, and substituted and unsubstituted aryl, alkaryl and aralkyl radicals.

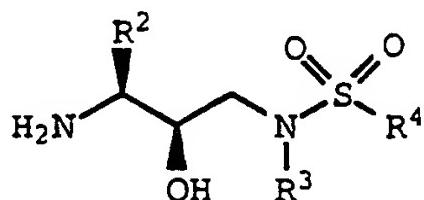
20 Examples of such suitable alcohols include benzyl alcohol, isopropyl alcohol, 4-methoxybenzyl alcohol, 2-trimethylsilylethanol, fluorenyl methanol and benzhydrol. Preferred alcohols are benzyl alcohol and 4-methoxybenzyl alcohol. Other primary and secondary alcohols suitable

25 for use in the practice of the present invention will be readily apparent to those skilled in the art.

The ester derivative is then saponified by any one of numerous well-known procedures, such as by

30 treatment with aqueous lithium hydroxide/THF (tetrahydrofuran), preferably for three hours at 0°C. The resultant product is the corresponding carbamate-

protected β -amino acids. These are subsequently deprotected by any one of several well-known procedures, such as by acid catalyzed hydrolysis or by hydrogenolysis, to produce the corresponding deprotected 5 β -amino acids. Alternatively, the carbamate-protected β -amino acid can be coupled to the amine



followed by deprotection and incorporation of R and R'.

10

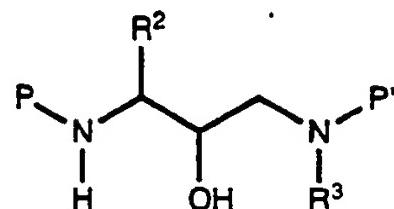
The N-protecting group can be subsequently removed, if desired, utilizing the procedures described above, and then reacted with a carboxylate represented by



the formula $\text{R}-\text{C}(=\text{O})-\text{L}$, wherein R is as defined above and 15 L is an appropriate leaving group such as a halide. Preferably, where R¹ is a side chain of a naturally occurring α -amino acid, R is a 2-quinoline carbonyl group occurring from N-hydroxysuccinimide-2-quinoline carboxylate, i.e., L is hydroxy succinimide. A solution 20 of the free amine (or amine acetate salt) and about 1.0 equivalent of the carboxylate are mixed in an appropriate solvent system and optionally treated with up to five equivalents of a base such as, for example, N-methylmorpholine, at about room temperature. Appropriate 25 solvent systems include tetrahydrofuran, methylene chloride or N,N-dimethyl formamide, and the like, including mixtures thereof.

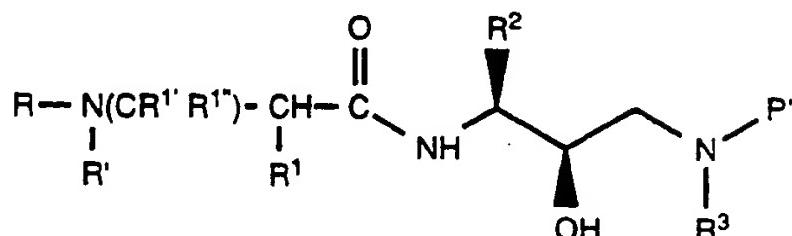
Alternatively, the protected amino alcohol from 30 the epoxide opening can be further protected at the newly introduced amino group with a protecting group P' which is not removed when the first protecting P is removed. One skilled in the art can choose appropriate combinations of P

and P'. One suitable choice is when P is Cbz and P' is Boc. The resulting compound represented by the formula:



5

can be carried through the remainder of the synthesis to provide a compound of the formula:



10

and the new protecting group P' is selectively removed, and following deprotection, the resulting amine reacted to form the sulfonamide derivative as described above. This selective deprotection and conversion to the sulfonamide 15 can be accomplished at either the end of the synthesis or at any appropriate intermediate step if desired.

The thiocarbonyl compounds of this invention are really prepared by methods well known to those skilled in the art, for example, by treatment of a carbonyl compound with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) which is an article of commerce. Phosphorus pentasulfide may also be used or one can treat an amine 25 of this invention with a pre-formed thiocarbonyl reagent such as thiocarbonylchlorid in the presence of base.

In place of the sulfonyl halides, sulfinyl halides (RSOCl) and sulfenyl halides (RSCl) can be 30 utilized to prepare compounds wherein the $-\text{SO}_2-$ moiety is replaced by $-\text{SO}-$ or $-\text{S}-$, respectively.

It is contemplated that for preparing compounds of the Formulas having R⁶, the compounds can be prepared following the procedure set forth above and, prior to 5 coupling the sulfonamide derivative or analog thereof, e.g. coupling to the amino acid PNH(CH₂)_tCH(R¹)COOH, carried through a procedure referred to in the art as reductive amination. Thus, a sodium cyanoborohydride and an appropriate aldehyde or ketone can be reacted with the 10 sulfonamide derivative compound or appropriate analog at room temperature in order to reductively aminate any of the compounds of Formulas I-IV. It is also contemplated that where R³ of the amino alcohol intermediate is hydrogen, the inhibitor compounds of the present 15 invention wherein R³ is alkyl, or other substituents wherein the α-C contains at least one hydrogen, can be prepared through reductive amination of the final product of the reaction between the amino alcohol and the amine or at any other stage of the synthesis for preparing the 20 inhibitor compounds.

Contemplated equivalents of the general formulas set forth above for the antiviral compounds and derivatives as well as the intermediates are compounds 25 otherwise corresponding thereto and having the same general properties, such as tautomers thereof as well as compounds, wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than 30 that indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not 35 critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

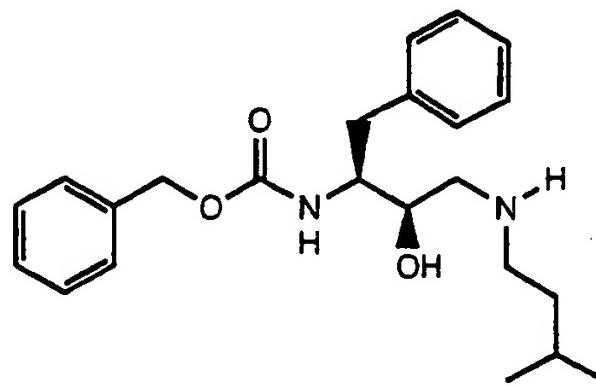
Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

All reagents were used as received without purification. All proton and carbon NMR spectra were obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

The following Examples 1 through 9 illustrate preparation of intermediates. These intermediates are useful in preparing the inhibitor compounds of the

present invention as illustrated in Examples 10-16. In addition, the intermediates of Examples 2-6 are also retroviral protease inhibitors and inhibit, in particular, HIV protease.

5

Example 1A10 Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isoamylaminePart A:

- To a solution of 75.0g (0.226 mol) of
15 N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone
in a mixture of 807 mL of methanol and 807 mL of
tetrahydrofuran at -2°C, was added 13.17g (0.348 mol,
1.54 equiv.) of solid sodium borohydride over one hundred
minutes. The solvents were removed under reduced
20 pressure at 40°C and the residue dissolved in ethyl
acetate (approx. 1L). The solution was washed
sequentially with 1M potassium hydrogen sulfate,
saturated sodium bicarbonate and then saturated sodium
chloride solutions. After drying over anhydrous
25 magnesium sulfate and filtering, the solution was removed
under reduced pressure. To the resulting oil was added
hexane (approx. 1L) and the mixture warmed to 60°C with
swirling. After cooling to room temperature, the solids
were collected and washed with 2L of hexane. The
30 resulting solid was recrystallized from hot ethyl acetate
and hexane to afford 32.3g (43% yield) of

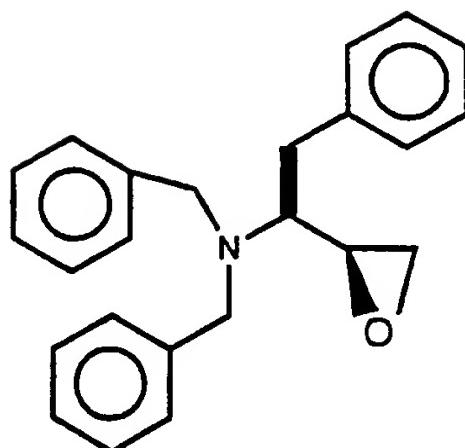
N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and M+Li⁺ = 340.

Part B:

5 To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent was removed
10 under reduced pressure and the solids dissolved in methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3g (77% yield)
15 of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and MH⁺ 298.

Part C:

A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours.
The solution was cooled to room temperature, concentrated in vacuo and then poured into 100 mL of stirring hexane
25 whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 1.18g, 95% of N=[(3(S)-phenylmethylcarbamoyl)amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0-109.5°C, MH⁺ m/z = 371.

Example 1B

5 Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane

Step A:

A solution of L-phenylalanine (50.0 g, 0.302 mol),
10 sodium hydroxide (24.2 g, 0.605 mol) and potassium
carbonate (83.6 g, 0.605 mol) in water (500 ml) was
heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) was
then slowly added (addition time ~25 min). The mixture
was then stirred at 97°C for 30 minutes. The solution
15 was cooled to room temperature and extracted with toluene
(2 x 250 ml). The combined organic layers were then
washed with water, brine, dried over magnesium sulfate,
filtered and concentrated to give an oil product. The
crude product was then used in the next step without
20 purification.

Step B:

The crude benzylated product of the above step was
dissolved in toluene (750 ml) and cooled to -55°C. A 1.5
25 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol)
was then added at a rate to maintain the temperature
between -55° to -50°C (addition time - 1 hour). The
mixture was stirred for 20 minutes at -55°C. The
reaction was quenched at -55°C by the slow addition of

methanol (37 ml). The cold solution was then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid (approx. 138 g) was filtered off and washed with toluene. The solid material was suspended in a mixture 5 of toluene (400 ml) and water (100 ml). The mixture was cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid was dissolved. The toluene layer was separated from the aqueous phase and washed with water and brine, dried over 10 magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) were then added to the residue upon which the alcohol product began to crystallize. After 30 min., an additional 50 ml hexane was added to promote further 15 crystallization. The solid was filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of material could be isolated by refiltering the mother liquor. The solids were combined and recrystallized from ethyl acetate (20 ml) and hexane 20 (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors were combined and concentrated (34 g). The residue was treated with ethyl acetate and hexane which provided an additional 7 g (~7% yield) of slightly 25 impure solid product. Further optimization in the recovery from the mother liquor is probable.

Alternatively, the alcohol was prepared from L-phenylalaninol. L-phenylalaninol (176.6 g, 1.168 mol) 30 was added to a stirred solution of potassium carbonate (484.6 g, 3.506 mol) in 710 mL of water. The mixture was heated to 65°C under a nitrogen atmosphere. A solution of benzyl bromide (400 g, 2.339 mol) in 3A ethanol (305 mL) was added at a rate that maintained 35 the temperature between 60-68°C. The biphasic solution was stirred at 65°C for 55 min and then allowed to cool to 10°C with vigorous stirring. The

oily product solidified into small granules. The product was diluted with 2.0 L of tap water and stirred for 5 minutes to dissolve the inorganic by products. The product was isolated by filtration under reduced pressure and washed with water until the pH is 7. The crude product obtained was air dried overnite to give a semi-dry solid (407 g) which was recrystallized from 1.1 L of ethyl acetate/heptane (1:10 by volume). The product was isolated by filtration (at -8°C), washed with 1.6 L of cold (-10°C) ethyl acetate/heptane (1:10 by volume) and air-dried to give 339 g (88% yield) of BS-2-[Bis(phenylmethyl)amino]benzene-propanol, mp 71.5-73.0°C. More product can be obtained from the mother liquor if necessary. The other analytical characterization was identical to compound prepared as described above.

Step C:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) was cooled to -74°C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) was then slowly added at a rate to maintain the temperature at -74°C (addition time ~1.25 hr). The mixture was stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time ~20 min., temp. -75°C to -68°C). The solution was stirred at -78°C for 35 minutes. Triethylamine (41.2 ml, 0.295 mol) was then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture was stirred for 30 min. and then water (225 ml) was added. The dichloromethane layer was separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue was diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate was

concentrated to give the desired aldehyde product. The aldehyde was carried on to the next step without purification.

5 Temperatures higher than -70°C have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern oxidations are also possible.

10 Alternatively, the aldehyde was prepared as follows. (200 g, 0.604 mol) was dissolved in triethylamine (300 mL, 2.15 mol). The mixture was cooled to 12°C and a solution of sulfur trioxide/pyridine complex (380 g, 2.39 mol) in DMSO (1.6 L) was added at a rate to maintain the
15 temperature between 8-17°C (addition time - 1.0 h). The solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hour at which time the reaction was complete by TLC analysis (33% ethyl acetate/hexane, silica gel). The reaction mixture was
20 cooled with ice water and quenched with 1.6 L of cold water (10-15°C) over 45 minutes. The resultant solution was extracted with ethyl acetate (2.0 L), washed with 5% citric acid (2.0 L), and brine (2.2 L), dried over MgSO₄ (280 g) and filtered. The solvent was removed on a
25 rotary evaporator at 35-40°C and then dried under vacuum to give 198.8 g of αS-[Bis-(phenylmethyl)amino]-benzenepropanaldehyde as a pale yellow oil (99.9%). The crude product obtained was pure enough to be used directly in the next step without purification. The
30 analytical data of the compound were consistent with the published literature. [α]_D25 = -92.9 ° (c 1.87, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ, 2.94 and 3.15 (ABX-System, 2H, J_{AB}= 13.9 Hz, J_{AX}= 7.3 Hz and J_{BX} = 6.2 Hz), 3.56 (t, 1H, 7.1 Hz), 3.69 and 3.82 (AB-System, 4H, J_{AB}= 13.7
35 Hz), 7.25 (m, 15 H) and 9.72 (s, 1H); HRMS calcd for (M+1) C₂₃H₂₄NO 330.450, found: 330.1836. Anal. Calcd. for C₂₃H₂₃ON: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.64; H,

7.42; N, 4.19. HPLC on chiral stationary phase: (S,S) Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of the desired S-isomer: 8.75 min., retention time of the R-enanatiomer 10.62 min.

Step D:

A solution of α S-[Bis(phenylmethyl)amino] benzene-propanaldehyde (191.7 g, 0.58 mol) and chloroiodomethane (56.4 mL, 0.77 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 365 mL, 0.58 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional chloroiodomethane (17 mL) was added, followed by n-butyllithium (110 mL) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. (2) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (55 mL, 0.088 mol) at <-25°C. After addition, the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (37 mL, 0.059 mol) at <-25°C. After addition, the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The

reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The 5 mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium 10 sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material. (The crude product weight was >100%. Due to the relative instability of the product on 15 silica gel, the crude product is usually used directly in the next step without purification). The diastereomeric ratio of the crude mixture was determined by proton NMR: (2S)/(2R): 86:14. The minor and major epoxide diastereomers were characterized in 20 this mixture by tlc analysis (silica gel, 10% ethyl acetate/hexane), R_f = 0.29 & 0.32, respectively. An analytical sample of each of the diastereomers was obtained by purification on silica-gel chromatography (3% ethyl acetate/hexane) and characterized as 25 follows:

N,N, α S-Tris(phenylmethyl)-2S-oxiranemethanamine

¹H NMR (400 MHz, CDCl₃) δ 2.49 and 2.51 (AB-System, 30 1H, J_{AB} = 2.82), 2.76 and 2.77 (AB-System, 1H, J_{AB} = 4.03), 2.83 (m, 2H), 2.99 & 3.03 (AB-System, 1H, J_{AB} = 10.1 Hz), 3.15 (m, 1H), 3.73 & 3.84 (AB-System, 4H, J_{AB} = 14.00), 7.21 (m, 15H); ¹³C NMR (400 MHz, CDCl₃) δ 139.55, 129.45, 128.42, 128.14, 128.09, 126.84, 35 125.97, 60.32, 54.23, 52.13, 45.99, 33.76; HRMS calcd for C₂₄H₂₆NO (M+1) 344.477, found 344.2003.

N,N, α S-Tris(phenylmethyl)-2R-oxiranemethanamine

1H NMR (300 MHz, CDCl₃) δ 2.20 (m, 1H), 2.59 (m, 1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85 (AB-System, 4H), 7.25 (m, 15H). HPLC on chiral stationary phase: Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of (8): 9.38 min., retention time of enantiomer of (4): 13.75 min.

Alternatively, a solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) was cooled to -78°C, under a nitrogen atmosphere. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) was then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) was added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture was stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) were added 4 more times over 45 min. at -75°C. The cooling bath was then removed and the solution warmed to 22°C over 1.5 hr. The mixture was poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer was separated. The aqueous phase was extracted with ethyl acetate (1 x 300 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be

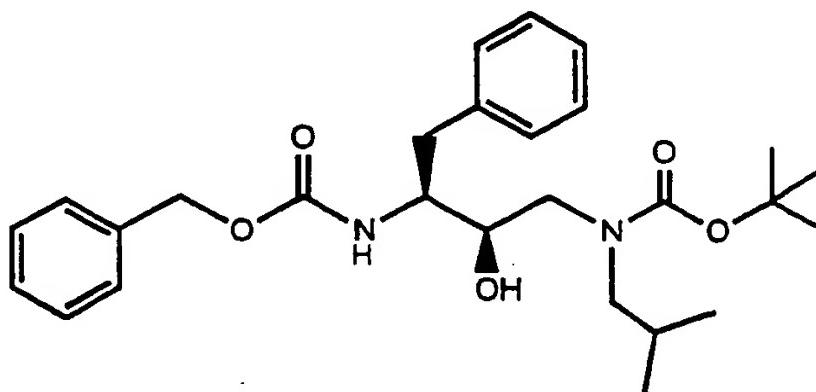
purified by recrystallization at a subsequent step. The product could also be purified by chromatography.

Alternatively, a solution of α S-

5 [Bis(phenylmethyl)amino]benzene-propanaldehyde (178.84 g, 0.54 mol) and bromochloromethane (46 mL, 0.71 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large
10 scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 340 mL, 0.54 mol) was then added at a rate that maintained the temperature below -25°C.
After addition the mixture was stirred at -30 to -35°C
15 for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional bromochloromethane (14 mL) was added, followed by n-butyllithium (102 mL) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10
20 minutes. This was repeated once. (2) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times.
25 (3) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture
30 warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving
35 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous

layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material.

10

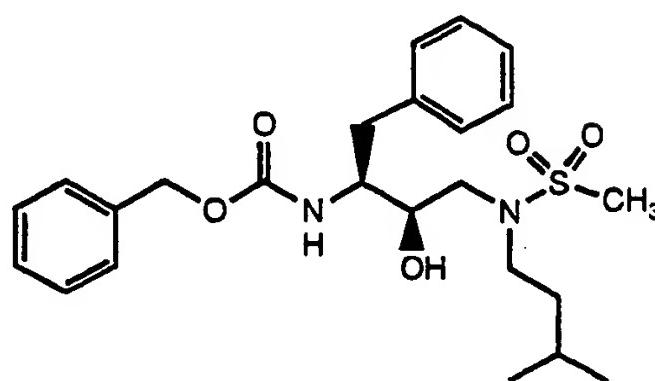
Example 2

15 Preparation of N-[3S-(phenylmethylcarbamoyl)amino]-2R-
hydroxy-4-phenyl-1-[(2-methylpropyl)amino]-2-(1,1-
dimethylethoxy)carbonyl]butane

To a solution of 7.51g (20.3 mmol) of N-[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenylbutyl-
 20 N-(2-methylpropyl)amine in 67 mL of anhydrous tetrahydrofuran was added 2.25g (22.3 mmol) of triethylamine. After cooling to 0°C, 4.4g (20.3 mmol) of di-tert-butyl dicarbonate was added and stirring continued at room temperature for 21 hours. The volatiles were
 25 removed in vacuo, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 9.6g of crude product. Chromatography on silica gel using 30% ethyl acetate/hexane afforded 8.2g
 30 of pure N-[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-

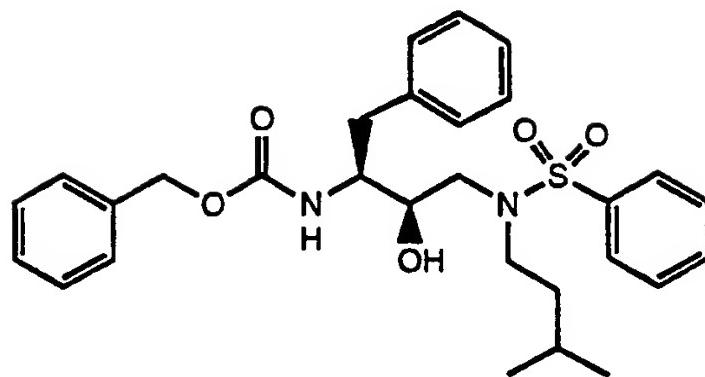
4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxy)carbonyl]butane, mass spectrum m/e = 477 (M+Li).

5

Example 3A

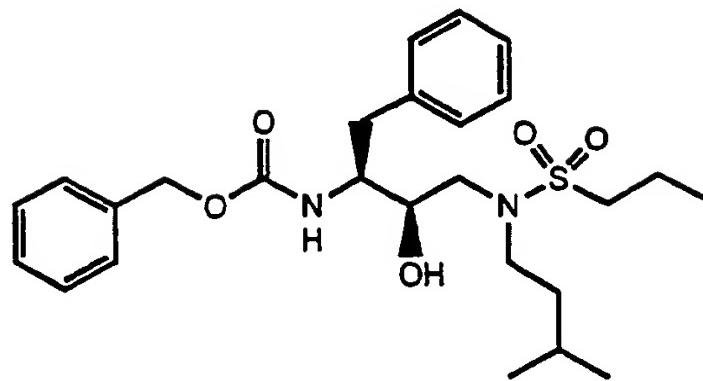
Preparation of phenylmethyl [2R-hydroxy-3-[(3-
10 methylbutyl) (methylsulfonyl)aminol]-1S-
(phenylmethyl)propyl]carbamate

To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (2.0 gm, 5.2 mmol) and triethylamine (723 uL, 5.5 mmol) in dichloromethane (20 mL) was added dropwise methanesulfonyl chloride (400 uL, 5.2 mmol). The reaction mixture was stirred for 2 hours at room temperature, then the dichloromethane solution was concentrated to ca. 5 mL and applied to a silica gel column (100 gm). The column was eluted with chloroform containing 1% ethanol and 1% methanol. The phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was obtained as a white solid Anal. Calcd for C₂₄H₃₄N₂O₅S: C, 62.31; H, 7.41; N, 6.06. Found: C, 62.17; H, 7.55; N, 5.97.

Example 3B

5 Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)phenylsulfonyl]amino]-1S-(phenylmethyl)propyl carbamate

From the reaction of N[3(S)-
10 benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]
N-isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528
uL, 3.8 mmol) and benzenesulfonyl chloride (483 uL, 3.8
mmol) one obtains phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)phenylsulfonyl]amino]-1S-(phenylmethyl)propyl carbamate. Column chromatography on silica gel eluting with chloroform containing 1% ethanol afforded the pure product. Anal. Calcd for C₂₉H₃₆N₂O₅S: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37;
H, 6.93; N, 5.26.

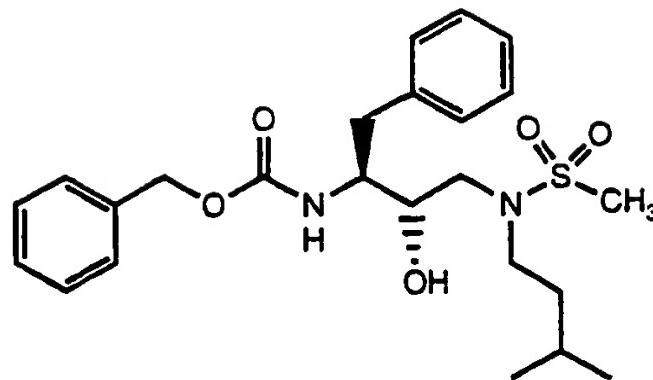
Example 4

5 Preparation of Phenylmethyl [2R-hydroxy-3-[1-(3-
methylbutyl) (n-propanesulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate

To a solution of N[3(S)-benzyloxycarbonylamino-
10 2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (192 mg , 0.5
mmol) and triethylamine (139 uL, 1.0 mmol) in
dichloromethane (10 mL) was added dropwise trimethylsilyl
chloride (63 uL, 0.5 mmol). The reaction was allowed to
stir for 1 hour at room temperature, cooled to 0° C with
15 an ice bath and then n-propanesulfonyl chloride (56 uL,
0.5 mmol) was added dropwise. The reaction mixture was
stirred for 1.5 hours at room temperature, then diluted
with ethyl acetate (50 mL) and washed sequentially with
1N HCl, water, saturated sodium bicarbonate solution, and
20 saturated sodium chloride solution (25 mL each). The
organic solution was dried over magnesium sulfate,
filtered and concentrated to an oil. The oil was stirred
with methanol (10 mL) for 16 hours, concentrated and the
residue chromatographed on silica gel (50 gm) eluting
25 with 10% ethyl acetate in hexane (450 mL), then with 1:1
ethyl acetate / hexane. The phenylmethyl [2R-hydroxy-3-
[(3-methylbutyl) (n-propanesulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate was recrystallized from
ethyl ether / hexane to afford a white solid Anal. Calcd.
30 for C₂₆H₃₈N₂O₅S: C, 63.64; H, 7.81; N, 5.71. Found: C,
63.09; H, 7.74; N, 5.64.

Example 5

5



The procedure described in Example 2 was used to prepare phenylmethyl [2S-hydroxy-3-[(3-methylbutyl) 10 (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate.

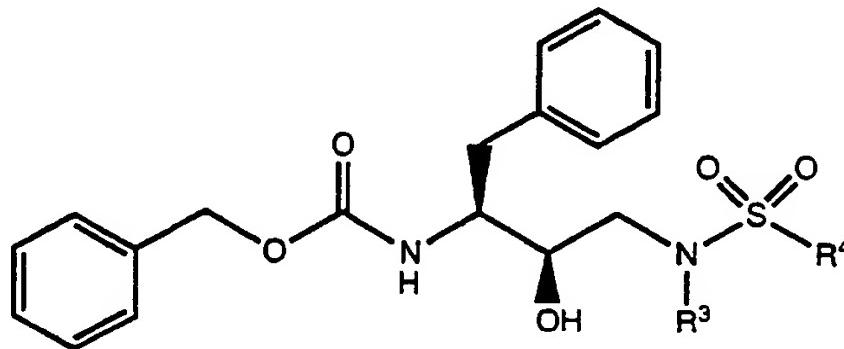
To a solution of N[3(S)-benzyloxycarbonylamino-2(S)-hydroxy-4-phenylbutyl] N-isoamylamine (192 mg, 0.5 mmol) and triethylamine (139 uL, 0.55 mmol) in dichloromethane 15 (8 mL) was added dropwise methanesulfonyl chloride (39 uL, 0.55 mmol). The reaction mixture was stirred for 16 hours at room temperature, then the dichloromethane solution was applied to a silica gel column (50 gm). The column was eluted with dichloromethane containing 2.5% methanol. The phenylmethyl [2S-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was obtained as a white solid Anal. Calcd. for C₂₄H₃₄N₂O₅S + 0.2 H₂O: C, 61.83; H, 7.44; N, 6.01. Found: C, 61.62; H, 7.40; N, 5.99.

Example 6

Following the procedures of the previous Examples 1-5,
the compounds set forth in Tables 1A and 1B were
5 prepared.

TABLE 1A

10



Entry	R ³	R ⁴
15	1 isoamyl	p-fluorophenyl
	2 isoamyl	p-nitrophenyl
	3 isoamyl	o-nitrophenyl
	4 isoamyl	β-naphthyl
	5 isoamyl	2-thienyl
20	6 isoamyl	benzyl
	7 isobutyl	p-fluorophenyl
	8 p-fluorobenzyl	phenyl
	9 4-pyridylmethyl	phenyl
	10 cyclohexylmethyl	phenyl
25	11 allyl	phenyl
	12 propyl	phenyl
	13 cyclopropylmethyl	phenyl
	14 methyl	phenyl
	15 propargyl	phenyl
30	16 isoamyl	p-chlorophenyl

TABLE 1A (Cont'd)

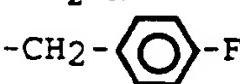
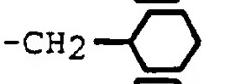
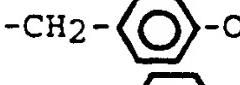
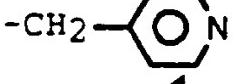
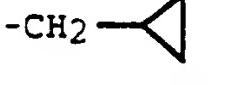
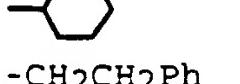
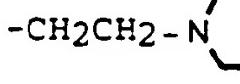
Entry	R ³	R ⁴
5		
17	isoamyl	p-methoxyphenyl
18	isoamyl	m-nitrophenyl
19	isoamyl	m-trifluoromethylphenyl
20	isoamyl	o-methoxycarbonylphenyl
10	21	isoamyl
	22	isobutyl
	23	-CH ₂ Ph
	24	-CH ₂ -  -
	25	-CH ₂ -  -
15	26	-CH ₂ -  -
	27	-CH ₂ -  -
	28	-CH ₂ - 
	29	-CH ₂ CH=CH ₂
	30	- 
20	31	- 
	32	-CH ₂ CH ₂ Ph
	33	-CH ₂ CH ₂ CH ₂ CH ₂ OH
	34	-CH ₂ CH ₂ N(CH ₃) ₂
	35	-CH ₂ CH ₂ -N 
25	36	-CH ₃
	37	-CH ₂ CH ₂ CH ₂ SCH ₃
	38	-CH ₂ CH ₂ CH ₂ S(O)CH ₃
	39	-CH ₂ CH ₂ CH(CH ₃) ₂
	40	-CH ₂ CH ₂ CH(CH ₃) ₂
		-CH ₂ CH ₂ CH ₃

TABLE 1A (Cont'd)

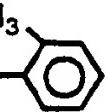
Entry	R ³	R ⁴
5	41 -CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₃
	42 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -F
	43 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -CH ₃
	44 -CH ₂ CH ₂ CH(CH ₃) ₂	CO ₂ CH ₃ 
10	45 -CH ₂ CH(CH ₃) ₂	-  -F
	46 -CH ₂ CH(CH ₃) ₂	-  -NHAC
	47 -CH ₂ CH(CH ₃) ₂	-  -CH ₃
	48 -CH ₂ CH ₂ CH ₃	-  -OCH ₃
	49 -CH ₂ CH ₂ CH ₂ CH ₃	-  -OCH ₃
15	50 -CH ₂ CH ₂ CH(CH ₃) ₂	-CF ₃
	51 -CH ₂ CH(CH ₃) ₂	-CH ₃
	52 -CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ Cl
	53 -CH ₂ CH(CH ₃) ₂	-CH ₂ =CH 
20	54 -CH ₂ CH(CH ₃) ₂	-  -OCH ₃
	55 -CH ₂ CH(CH ₃) ₂	-CH=CH ₂
	56 -CH ₂ -CH(CH ₃)-CH ₃) (CH ₂ CH ₃)	-  -OCH ₃

TABLE 1A (Cont'd)

Entry		MASS MEASUREMENT			
		MOL FORM	CALC	FOUND	
1			C ₂₉ H ₃₆ N ₂ O ₅ S	531 (M+Li)	531
2			C ₂₉ H ₃₆ N ₂ O ₆ S	541(M+H)	541
3			C ₃₀ H ₃₆ N ₂ O ₆ S	555.2529 (M+H)	555.2582
4					
5					
6			C ₂₈ H ₃₃ N ₂ O ₅ SF	529.2172 (M+H)	521.2976
7					
8			C ₂₉ H ₃₆ N ₂ O ₅ S ₂	563 (M+Li)	563
9			C ₂₉ H ₃₆ N ₂ O ₆ S ₂	573(M+H)	573
5	10		C ₂₉ H ₃₆ N ₂ O ₇ S ₂	595 (M+Li)	595

TABLE 1B

5

Entry	R	R^3
1		$-CH_2Ph$
10		$-CH_2CH_2CH(CH_3)_2$
3		$-CH_2CH(CH_3)_2$
4		$-CH_2CH(CH_3)_2$
5		$-CH_2CH(CH_3)_2$

TABLE 1B (Cont'd)

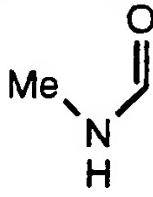
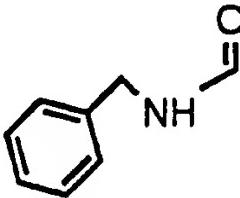
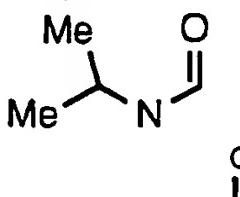
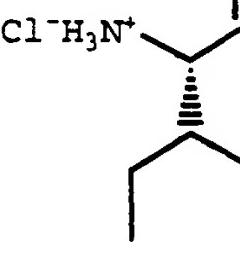
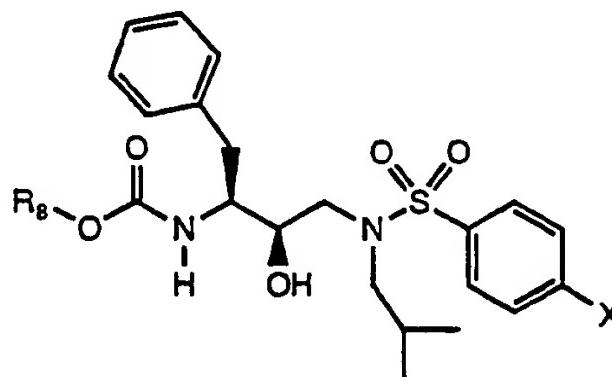
Entry	R	R^3
5		
6		$-\text{CH}_2\text{CH}(\text{CH}_3)_2$
7		$-\text{CH}_2\text{CH}(\text{CH}_3)_2$
8		$-\text{CH}_2\text{CH}(\text{CH}_3)_2$
9		$-\text{CH}_2\text{CH}_2(\text{CH}_3)_2$
10		

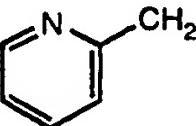
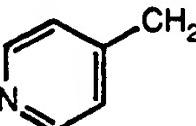
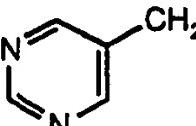
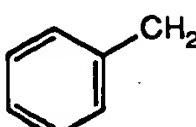
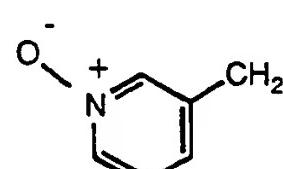
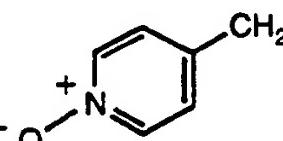
Table 1C

5

X	R ⁸	FORMULA	Mass Determination	
			Calc	Found
H		C ₂₇ H ₃₃ N ₃ O ₅ S	512.2219(M+H)	521.2267
OCH ₃		C ₂₈ H ₃₅ N ₃ O ₆ S	548.2407(M+Li)	548.2434
F		C ₂₇ H ₃₂ N ₃ O ₅ SF	530(M+H)	530
Cl		C ₂₇ H ₃₂ N ₃ O ₅ SCl	546(M+H)	546
NO ₂		C ₂₇ H ₃₂ N ₄ O ₇ S	557(M+H)	557
OH		C ₂₇ H ₃₃ N ₃ O ₆ S	528(M+H)	528

10

TABLE 1C (Cont'd)

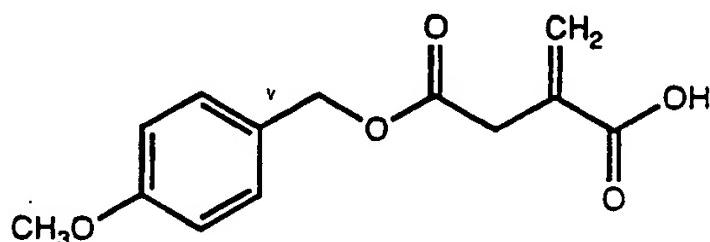
X	R ^B	FORMULA	Mass Determination	
			Calc	Found
5				
OCH ₃		C ₂₈ H ₃₅ N ₃ O ₆ S	542.2325(M+H)	542.2362
OCH ₃		C ₂₈ H ₃₅ N ₃ O ₆ S	548.2407(M+Li)	548.2393
OCH ₃		C ₂₈ H ₃₅ N ₃ O ₆ S	543(M+H)	543
OCH ₃		C ₂₉ H ₃₆ O ₆ N ₂ S	547.2454(M+Li)	547.2475
OCH ₃	tert-Butyl	C ₂₆ H ₃₈ N ₂ O ₆ S	513.2611(M+Li)	513.2593
OCH ₃		C ₂₈ H ₃₅ N ₃ O ₇ S	564(M+Li)	564
OCH ₃		C ₂₈ H ₃₅ N ₃ O ₇ S	564(M+Li)	564

The following Examples 7-9 illustrate preparation of β -amino acid intermediates. These intermediates can be coupled to the intermediate compounds of Examples 1-6 to produce inhibitor compounds of the present invention containing β -amino acids.

Example 7

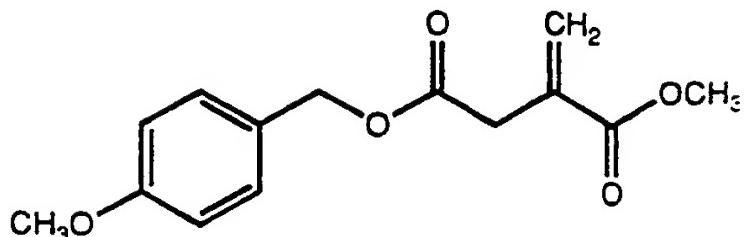
A. Preparation of 4(4-methoxybenzyl)itaconate

10



A 5 L three-necked round bottomed flask equipped with constant pressure addition funnel, reflux condenser, nitrogen inlet, and mechanical stirrer was charged with itaconic anhydride (660.8g, 5.88 mol) and toluene (2300 mL). The solution was warmed to reflux and treated with 4-methoxybenzyl alcohol (812.4g, 5.88 mol) dropwise over a 2.6h period. The solution was maintained at reflux for an additional 1.5h and then the contents were poured into three 2 L erlenmeyer flasks to crystallize. The solution was allowed to cool to room temperature whereupon the desired mono-ester crystallized. The product was isolated by filtration on a Buchner funnel and air dried to give 850.2g, 58% of material with mp 83-85°C, a second crop, 17% was isolated after cooling of the filtrate in an ice bath. ^1H NMR (CDCl_3) 300 MHz 7.32(d, $J=8.7$ Hz, 2H), 6.91(d, $J=8.7$ Hz, 2H), 6.49(s, 1H), 5.85(s, 1H), 5.12(s, 2H), 3.83(s, 3H), 3.40(s, 2H).

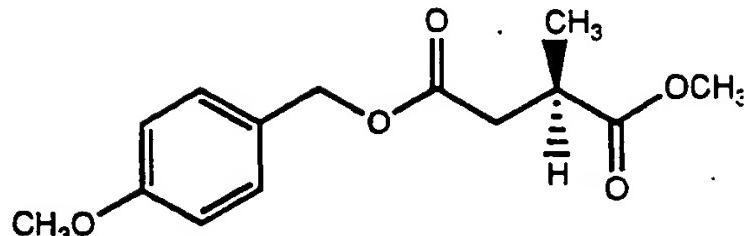
B. Preparation of Methyl 4(4-methoxybenzyl) itaconate



5 A 5 L three-necked round bottomed flask equipped with reflux condenser, nitrogen inlet, constant pressure addition funnel and mechanical stirrer was charged with 4(4-methoxybenzyl) itaconate (453.4g, 1.81 mol) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene
10 (275.6g, 1.81 mol), (DBN), dropwise so that the temperature did not rise above 15°C. To this stirring mixture was added a solution of methyl iodide (256.9g, 1.81 mol) in 250 mL of toluene from the dropping funnel over a 45m period. The solution was allowed to warm to
15 room temperature and stirred for an additional 3.25h.

The precipitated DBN hydroiodide was removed by filtration, washed with toluene and the filtrate poured into a separatory funnel. The solution was washed with
20 sat. aq. NaHCO₃ (2 X 500 mL), 0.2N HCl (1 X 500 mL), and brine (2 X 500 mL), dried over anhyd. MgSO₄, filtered, and the solvent removed in vacuo. This gave a clear colorless oil, 450.2g, 94% whose NMR was consistent with the assigned structure. ¹H NMR (CDCl₃) 300 MHz 7.30(d,
25 J=8.7 Hz, 2H), 6.90(d, J=8.7 Hz, 2H), 6.34(s, 1H), 5.71(s, 1H), 5.09(s, 2H), 3.82(s, 3H), 3.73(s, 3H), 3.38(s, 2H). ¹³C NMR (CDCl₃) 170.46, 166.47, 159.51, 133.55, 129.97, 128.45, 127.72, 113.77, 66.36, 55.12, 51.94, 37.64.

C. Preparation of Methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate



5

A 500 mL Fisher-Porter bottle was charged with methyl 4(4-methoxybenzyl) itaconate (71.1g, 0.269 mol), rhodium (R,R) DiPAMP catalyst (204mg, 0.269 mmol, 0.1 mol%) and degassed methanol (215 mL). The bottle was flushed 5 times with nitrogen and 5 times with hydrogen to a final pressure of 40 psig. The hydrogenation commenced immediately and after ca. 1h the uptake began to taper off, after 3h the hydrogen uptake ceased and the bottle was flushed with nitrogen, opened and the contents concentrated on a rotary evaporator to give a brown oil that was taken up in boiling iso-octane (ca. 200 mL, this was repeated twice), filtered through a pad of celite and the filtrate concentrated in vacuo to give 66.6g, 93% of a clear colorless oil, ^1H NMR (CDCl_3 300 MHz 7.30(d, 1H, $J=8.7$ Hz, 2H), 6.91(d, $J=8.7$ Hz, 2H), 5.08(s, 2H), 3.82(s, 3H), 3.67(s, 3H), 2.95(ddq, $J=5.7, 7.5, 8.7$ Hz, 1H), 2.79(dd, $J=8.1, 16.5$ Hz, 1H), 2.45(dd, $J=5.7, 16.5$ Hz, 1H), 1.23(d, $J=7.5$ Hz, 3H).

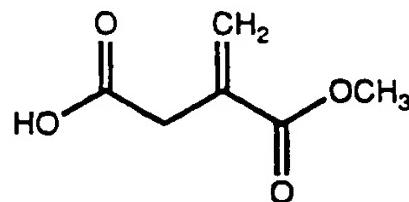
25 D. Preparation of Methyl 2(R)-methylsuccinate

A 3 L three-necked round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, reflux condenser and constant pressure addition funnel was charged with methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate (432.6g, 1.65 mol) and toluene (1200 mL). The stirrer was started and the solution treated with trifluoroacetic acid (600 mL) from the dropping funnel over 0.25h. The solution turned a deep purple color and the internal temperature rose to 45°C. After stirring

for 2.25h the temperature was 27°C and the solution had acquired a pink color. The solution was concentrated on a rotary evaporator. The residue was diluted with water (2200 mL) and sat. aq. NaHCO₃ (1000 mL). Additional 5 NaHCO₃ was added until the acid had been neutralized. The aqueous phase was extracted with ethyl acetate (2 X 1000 mL) to remove the by-products and the aqueous layer was acidified to pH=1.8 with conc. HCl. This solution was extracted with ethyl acetate (4 X 1000 mL), washed 10 with brine, dried over anhyd. MgSO₄, filtered and concentrated on a rotary evaporator to give a colorless liquid 251g, >100% that was vacuum distilled through a short path apparatus cut 1: bath temperature 120°C @ >1mm, bp 25-29°C; cut 2: bath temperature 140°C @ 0.5mm, 15 bp 95-108°C, 151g, $[\alpha]_d$ @ 25°C = +1.38°C (c=15.475, MeOH), $[\alpha]_d$ = +8.48°C (neat); cut 3: bath temperature 140°C, bp 108°C, 36g, $[\alpha]_d$ @ 25°C = +1.49°C (c=15.00, MeOH), $[\alpha]_d$ = +8.98°C (neat). Cuts 2 and 3 were combined to give 189g, 78% of product, ¹H NMR (CDCl₃) 300 MHz 11.6(brs, 20 1H), 3.72(s, 3H), 2.92(ddq, J=5.7, 6.9, 8.0 Hz, 1H), 2.81(dd, J=8.0, 16.8 Hz, 1H), 2.47(dd, J=5.7, 16.8 Hz, 1H), 1.26(d, J=6.9 Hz, 3H).

E. Preparation of Methyl Itaconate

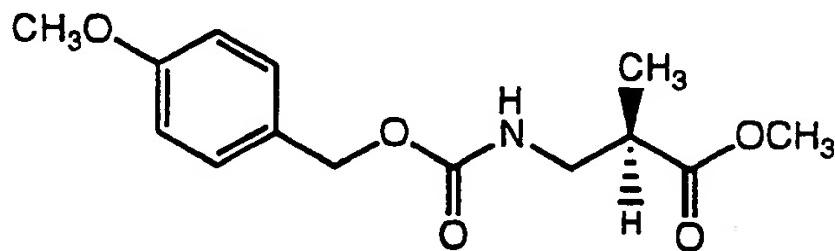
25



A 50 mL round bottomed flask equipped with reflux condenser, nitrogen inlet and magnetic stir bar 30 was charged with methyl 4(4-methoxybenzyl) itaconate (4.00g, 16 mmol), 12 mL of toluene and 6 mL of trifluoroacetic acid. The solution was kept at room temperature for 18 hours and then the volatiles were removed in vacuo. The residue was taken up in ethyl 35 acetate and extracted three times with saturated aqueous

sodium bicarbonate solution. The combined aqueous extract was acidified to pH=1 with aqueous potassium bisulfate and then extracted three times with ethyl acetate. The combined ethyl acetate solution was washed 5 with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was then vacuum distilled to give 1.23g, 75% of pure product, bp 85-87 @ 0.1 mm. ¹H NMR (CDCl₃) 300 MHz 6.34(s, 1H), 5.73(s, 2H), 3.76(s, 3H), 10 3.38(s, 2H). ¹³C NMR (CDCl₃) 177.03, 166.65, 129.220, 132.99, 52.27, 37.46.

F. Curtius Rearrangement of Methyl 2(R)-methylsuccinate:
15 Preparation of Methyl N-Moz- α -methyl β -alanine.

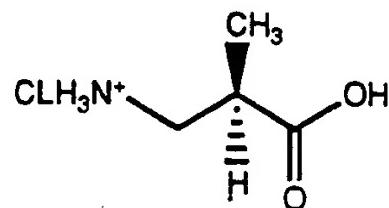


A 5L four necked round bottomed flask equipped 20 with a nitrogen inlet, reflux condenser, mechanical stirrer, constant pressure addition funnel, and thermometer adapter was charged with methyl 2(R)-methylsuccinate (184.1g, 1.26 mol), triethylamine (165.6g, 218 mL, 1.64 mol, 1.3 equivalents), and toluene 25 (1063 mL). The solution was warmed to 85°C and then treated dropwise with a solution of diphenylphosphoryl azide (346.8g, 1.26 mol) over a period of 1.2h. The solution was maintained at that temperature for an additional 1.0h and then the mixture was treated with 30 4-methoxybenzyl alcohol (174.1g, 1.26 mol) over a 0.33h period from the dropping funnel. The solution was stirred at 88°C for an additional 2.25h and then cooled to room temperature. The contents of the flask were poured into a separatory funnel and washed with sat. aq. 35 NaHCO₃ (2 x 500 mL), 0.2N HCl (2 x 500 mL), brine (1 x

500 mL), dried over anhyd. MgSO₄, filtered, and concentrated in vacuo to give 302.3g, 85% of the desired product as a slightly brown oil. ¹H NMR (CDCl₃) 300 MHz 7.32(d, J=8.4 Hz, 2H), 6.91(d, J=8.4 Hz, 2H), 5.2(brm, 5 1H), 5.05(s, 2H), 3.83(s, 3H), 3.70(s, 3H), 3.35(m, 2H), 2.70(m, 2H), 1.20(d, J=7.2 Hz, 3H).

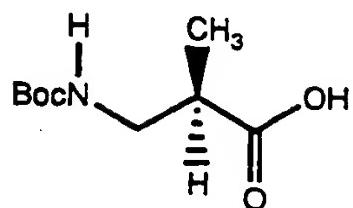
G. Hydrolysis of Methyl N-Moz- α -methyl β -alanine:
Preparation of α -methyl β -alanine Hydrochloride

10



A 5 L three-necked round bottomed flask equipped with a reflux condenser, nitrogen inlet and mechanical stirrer was charged with methyl N-Moz- α -methyl β -alanine (218.6g, 0.78 mol), glacial acetic acid (975 mL) and 12N hydrochloric acid (1960 mL). The solution was then heated to reflux for 3h. After the solution had cooled to room temperature (ca. 1h) the aqueous phase was decanted from organic residue (polymer) and the aqueous phase concentrated on a rotary evaporator. Upon addition of acetone to the concentrated residue a slightly yellow solid formed that was slurried with acetone and the white solid was isolated by filtration on a Buchner funnel.

The last traces of acetone were removed by evacuation to give 97.7g, 90% of pure product, mp 128.5-130.5°C [α]_d @ 25°C=9.0°C (c=2.535, Methanol). ¹H NMR (D₂O) 300 MHz 3.29(dd, J=8.6, 13.0 Hz, 1H), 3.16(dd, J=5.0, 13.0m Hz, 1H), 2.94(ddq, J=7.2, 5.0, 8.6 Hz, 1H), 1.30(d,J=7.2 Hz, 3H); ¹³C NMR (D₂O) 180.84, 44.56, 40.27, 17.49.

H. Preparation of N-Boc α -Methyl β -Alanine

5 A solution of α -methyl β -alanine hydrochloride (97.7g, 0.70 mol) in water (1050 mL) and dioxane (1050 mL) the pH was adjusted to 8.9 with 2.9N NaOH solution. This stirring solution was then treated with di-*tert*-butyl pyrocarbonate (183.3g, 0.84 mol, 1.2 equivalents)

10 all at once. The pH of the solution was maintained between 8.7 and 9.0 by the periodic addition of 2.5N NaOH solution. After 2.5h the pH had stabilized and the reaction was judged to be complete. The solution was concentrated on a rotary evaporator (the temperature was

15 maintained at <40°C). The excess di-*tert*-butyl pyrocarbonate was removed by extraction with dichloromethane and then the aqueous solution was acidified with cold 1N HCl and immediately extracted with ethyl acetate (4 X 1000 mL). The combined ethyl acetate extract was washed with brine, dried over anhyd. MgSO₄, filtered and concentrated on a rotary evaporator to give a thick oil 127.3g, 90% crude yield that was stirred with n-hexane whereupon crystals of pure product formed, 95.65g, 67%, mp 76-78°C, [α]_d @ 25°C = -11.8°C (c=2.4,

20 EtOH). A second crop was obtained by concentration of the filtrate and dilution with hexane, 15.4g, for a combined yield of 111.05g, 78%. ¹H NMR (acetone D₆) 300 MHz 11.7 (brs, 1H), 6.05 (brs 1H), 3.35 (m, 1H), 3.22 (m, 1H), 2.50 (m, 1H), 1.45(s, 9H), 1.19 (d, J=7.3 Hz, 3H);

25 ¹³C NMR (acetone D₆) 177.01, 79.28, 44.44, 40.92, 29.08, 15.50. Elemental analysis calc'd. for C₉H₁₇NO₄: C, 53.19, H, 8.42; N, 6.89. Found: C, 53.36; H, 8.46; N, 6.99.

30

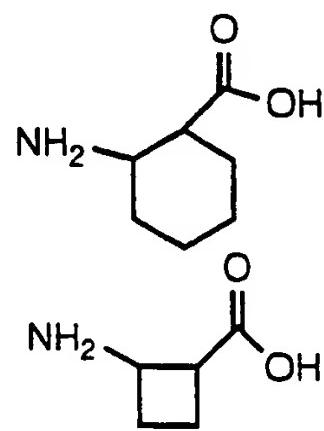
I. Preparation of N-4-Methoxybenzyloxycarbonyl α -Methyl β -Alanine

A solution of N-4-methoxybenzyloxycarbonyl
 5 α -methyl β -alanine methyl ester (2.81g, 10.0 mmol) in 30 mL of 25% aqueous methanol was treated with lithium hydroxide (1.3 equivalents) at room temperature for a period of 2h. The solution was concentrated in vacuo and the residue taken up in a mixture of water and ether and
 10 the phases separated and the organic phase discarded. The aqueous phase was acidified with aqueous potassium hydrogen sulfate to pH=1.5 and then extracted three times with ether. The combined ethereal phase was washed with saturated aqueous sodium chloride solution, dried over
 15 anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 2.60 g, 97% of N-4-Methoxybenzyloxycarbonyl α -methyl β -alanine (N-Moz-AMBA) which was purified by recrystallization from a mixture of ethyl acetate and hexane to give 2.44g, 91% of pure product, mp 96-97°C,
 20 $MH^+=268$. 1H NMR (D₆-acetone/300 MHz) 1.16 (3H, d, J=7.2Hz), 2.70 (1H, m), 3.31 (2H, m), 3.31 (3H, s), 4.99 (2H, s), 6.92 (2H, 4, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz).

Example 8

25

Utilizing generally the procedure set forth in Example 7, the following β -amino acid compounds were prepared.

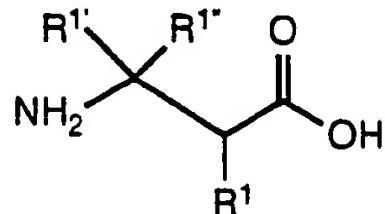


30

Example 9

Following generally the procedure of Example 7,
the β -amino acids set forth in Table 2 were prepared.

5

Table 2

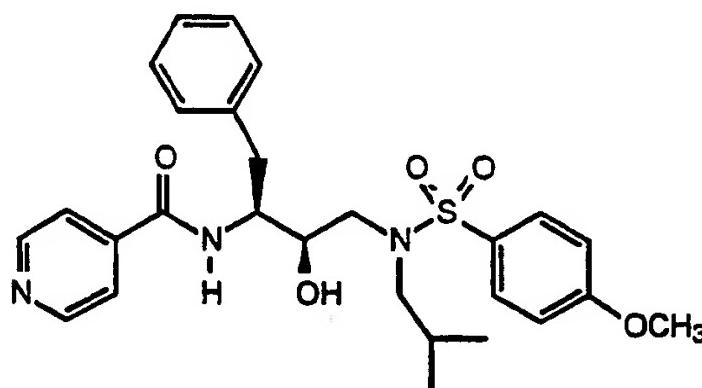
10

	Entry	R ¹	R ^{1'}	R ^{1''}
15	1	-CH ₃	H	H
	2	-CH(CH ₃) ₂	H	H
	3	-C(CH ₃) ₃	H	H
	4	H	H	H
	5	H	-CH ₃	H
	6	H	-CH ₃	-CH ₃
20	7	H	H	-CO ₂ CH ₃
	8	H	H	-CONH ₂
	9	-CH ₂ CH ₃	H	H
	10	-CH ₂ CH(CH ₃) ₂	H	H
	11	-CH ₂ C ₆ H ₅	H	H
	12	-CH ₂ --OH	H	H
25	13	-CH ₂ -	H	H
	14	-CH ₂ COOH	H	H
	15	H	-CH(CH ₃) ₂	H
	16	H	-CH ₂ CH(CH ₃) ₂	H
	17	H	-CH ₂ -	H

Table 2 (Cont'd)

Entry	R ¹	R ^{1'}	R ^{1''}
5			
18	H	-CH ₂ CH ₂ - 	H
19	H	- (CH ₂) ₃ - 	H
20	H	- (CH ₂) ₄ - 	H
21	H	- (CH ₂) ₃ CH(C ₆ H ₅) ₂	H

10

Example 10A

15

Preparation of 4-Pyridinecarboxamide,
N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl

20 To a solution of 231 mg (0.57 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 3 mL of methylene chloride at 0 C, was added 288 mg (2.85 mmol) of triethylamine and then 112 mg (0.63 mmol) of isonicotinoyl chloride hydrochloride. After 19 hours at room temperature, the solvent was removed, ethyl acetate added, then washed with saturated sodium bicarbonate, brine, dried with magnesium sulfate, filtered and concentrated to afford 290 mg of crude product. This was chromatographed on silica gel using 3-5% isopropanol/methylene chloride as eluent to afford 190 mg

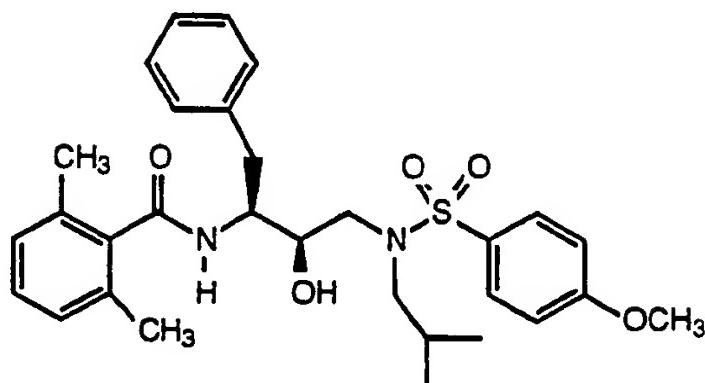
25

30

of the desired compound; mass spectrum calc. for C₂₇H₃₄N₃O₅S (M + H) 512.2219; found 512.2280.

Example 10B

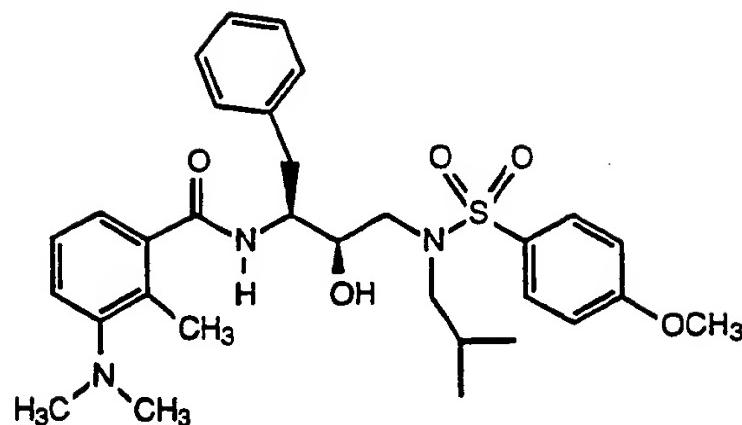
5



Preparation of Benzamide.

10 N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl]-2,6-dimethyl-

To a solution of 83 mg (0.55 mmol) of 2,6-dimethylbenzoic acid and 125 mg (0.82 mmol) of N-hydroxybenzotriazole in 3 mL of anhydrous DMF at 0°C was added 117 mg (0.61 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After 2 hours at 0°C, 203 mg (0.50 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 22 hours at room temperature, the solvent was removed in vacuo, ethyl acetate added, then washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 300 mg of crude product. Chromatography on silica gel using 20-50% ethyl acetate/hexane afforded 37 mg of the desired product; mass spectrum calcd for C₃₀H₃₈N₂O₅S (M+H) 539.2580; found 539.2632.

Example 10C

- 5 Preparation of Benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-2-methyl.

Part A. Preparation of 4-Nitro-2-methylbenzoic Acid.

10

A mixture of 1.0 g (3.8 mmol) of 2-iodo-nitrotoluene, 2.1 g (15.2 mmol) potassium carbonate and 27 mg (0.038 mmol) of palladium(II) dichloride bis(triphenylphosphine) in a mixture of 5mL of water and 10 mL of N,N-

15 dimethylformamide. This was placed in a Fisher/Porter bottle under 15 psig of carbon monoxide and heated at 70°C for 16 hours. The solution became homogeneous when heated. The reaction was cooled, diethyl ether and water was added, the organic layer separated and discarded.

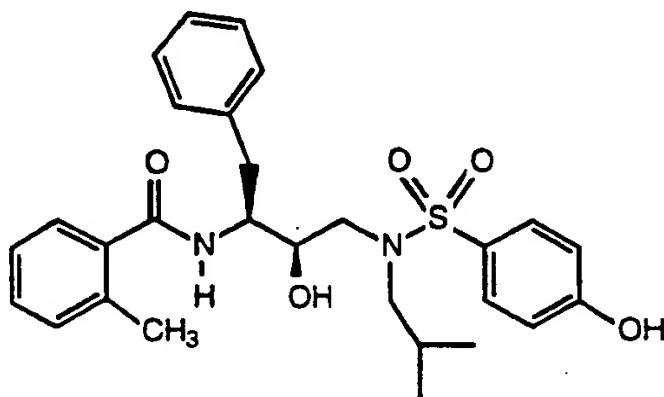
20 The aqueous layer was acidified with 1N hydrochloric acid, extracted with ethyl acetate, washed with water, brine, dried over magnesium sulfate, filtered and concentrated to yield 0.5g of crude material. This dissolved in ethyl acetate, hexane added and the resulting brown solid 25 discarded. The filtrate was concentrated, and then recrystallized from diethyl ether/hexane to afford 215mg of 4-nitro-2-methylbenzoic acid, m/e=182 (M+H).

Part B. Preparation of Benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-2-methyl-4-nitro.

- To a solution of 181mg (1.0mmol) of 4-nitro-2-methylbenzoic acid and 230mg (1.5mmol) N-hydroxybenzotriazole in 3mL of anhydrous N,N-dimethylformamide at 0°C, was added 211mg (1.1mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring at 0 C for 1 hour, 406mg (1mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 17 hours at room temperature, the solvent was removed under reduced pressure, ethyl acetate added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried with magnesium sulfate, filtered and concentrated to yield 0.55g of crude product. This was chromatographed on silica gel using 20-50% ethyl acetate/hexane as eluent to afford 0.49g of the desired benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-nitro, m/e=570 (M+H).
Part C. Preparation of Benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-amino.
A solution of 400mg (0.70mmol) of benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-nitro from part B in 20mL of methanol was hydrogenated over 0.2 g of 10% palladium on carbon catalyst under 50 psig of hydrogen for 2.5 hours. The catalyst was removed by filtration and the solution concentrated to afford 370mg of the desired benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-amino, m/e=540 (M+H).
Part D. Preparation of Benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-dimethylamino.

A solution of 0.17g (0.31mmol) of benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-amino from part C in 5mL of methanol and 0.20mL of 37% aqueous formaldehyde was hydrogenated over 90mg of 10% palladium on carbon under 15psig of hydrogen for 16 hours. The catalyst was removed by filtration, the solvents removed under reduced pressure to afford 0.16g of crude material. Chromatography on silica gel using 50% ethyl acetate as eluent afforded 0.12g of the desired benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-4-dimethylamino, m/e=568 (M+H).

15

Example 10D

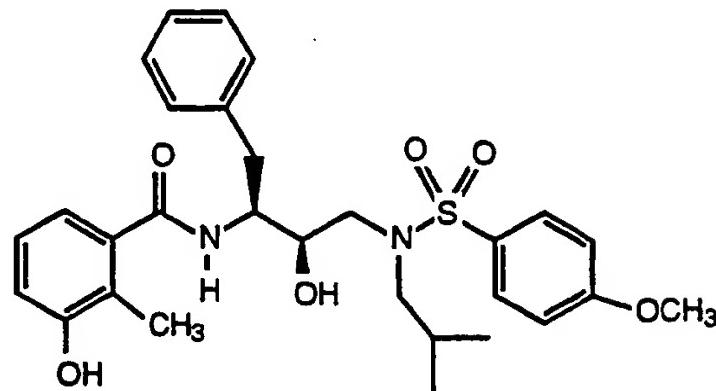
20 Preparation of Benzamide, N-[2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl-

To a solution of 500 mg (1mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 2 mL of methylene chloride and 2 mL of N,N-dimethylformamide, was added 0.42 mL of triethylamine, followed by 0.12 mL of ortho-toluoyl chloride. After 17 hours, the solvent was removed under reduced pressure, the residue dissolved in ethyl acetate, was washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered

and concentrated to afford 490 mg of crude material. This was chromatographed over 100g of silica gel using 20-50% ethyl acetate/hexane as eluent to afford 232 mg of the desired product, m/e=511(M+H).

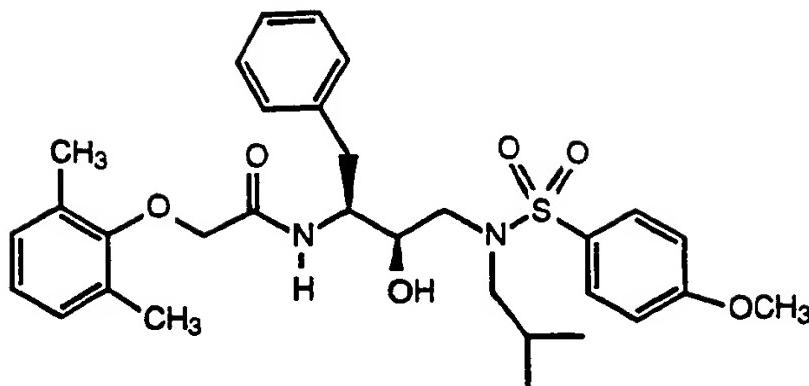
5

Example 10E



- 10 Preparation of Benzamide, N-[2R-hydroxy-3-[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-3-hydroxy-2-methyl

To a solution of 131 mg (0.86 mmol) of 3-hydroxy-2-methylbenzoic acid and 305 mg (0.75 mmol) of N-hydroxybenzotriazole in 4 mL of anhydrous N,N-dimethylformamide at 0°C, was added 165 mg (0.86 mmol) of EDC. After 20 minutes of activation at 0°C and 1 hour at room temperature, 305 mg (0.75 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 460 mg of crude material. This was chromatographed on silica gel using 0-35% ethyl acetate/methylene chloride as eluent to afford 250 mg of pure benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-3-hydroxy-2-methyl, m/e = 547(M+Li).

Example 10F

- 5 Preparation of N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-(2,6-dimethylphenoxy)acetamide

Part A: Preparation of 2,6-Dimethylphenoxyacetic acid

10

2,6-Dimethylphenol (6.1 g, 50.0 mmol), bromoacetic acid (6.9 g, 50.0 mmol) and 2.5 N aqueous sodium hydroxide (50.0 mL, 125.0 mmol) were refluxed in water (125 mL) for 4 hrs. Bromoacetic acid (6.9 g, 50.0 mmol) and 2.5 N aqueous sodium hydroxide (20.0 mL, 62.5 mmol) were added and the solution refluxed for an additional 16 hrs. The solution was cooled to room temperature and water (200 mL) was added. The pH of the solution was adjusted to 1.0 with concentrated aqueous hydrochloric acid. The resulting precipitate was collected and recrystallized from ethyl acetate/hexanes (1:9, 700 mL). 2,6-Dimethylphenoxyacetic acid (4.53 g, 25.1 mmol, 50%) was collected as a white crystalline solid. ^1H NMR (CD_3OD) δ 2.26 (s, 6H), 4.38 (s, 2H), 6.90-7.00 (m, 3H).

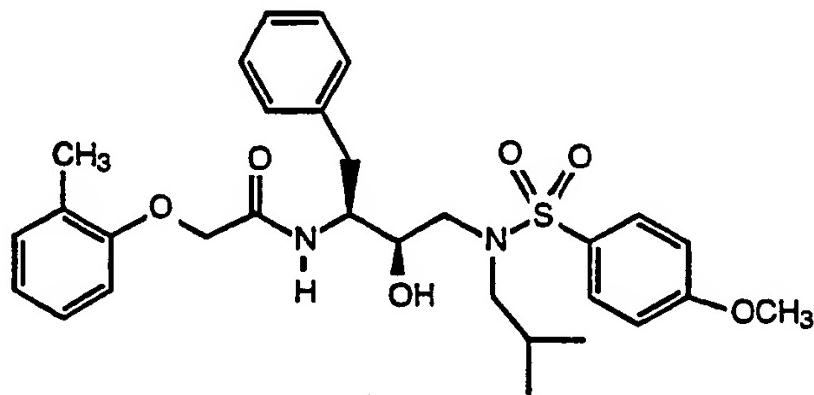
25

Part B: Preparation of N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-(2,6-dimethylphenoxy)acetamide

- 30 To a solution of 180.1 mg (0.83 mmol) of 2,6-(dimethylphenoxy)acetic acid in 10 mL of anhydrous methylene chloride at room temperature, was added 114 mg

(0.60 mmol) of EDC. After 15 minutes of activation, 203 mg of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxybenzene)sulfonyl]amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 16 hours the 5 solution was extracted with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 244 mg of crude product. A quantity of this (15 mg) was chromatographed on silica gel using 25% ethyl acetate/hexane to afford 8 10 mg of the desired compound, m/e=575 (M+Li).

Example 10G



15

Preparation of N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl]- (2-methylphenoxy)acetamide

20 Part A: Preparation of 2-Methylphenoxyacetic Acid.

2-Methylphenol (2.0 g, 18.4 mmol), bromoacetic acid (2.5 g, 18.4 mmol) and 2.5 N aqueous sodium hydroxide (25.0 mL, 62.55.0 mmol) refluxed for 16 hrs. The pH of the 25 solution was adjusted to 1 with concentrated aqueous hydrochloric acid. The resulting precipitate was collected triturated with hexanes. The 2-methylphenoxyacetic acid (720 mg, 4.33 mmol, 25%) was collected as a white crystalline solid. ^1H NMR (CD_3OD) δ 30 2.43 (s, 3H), 4.65 (s, 2H) 6.70-7.10 (m, 4H).

Part B: Preparation of N-[2R-hydroxy-3-[[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-(2-methylphenoxy)acetamide

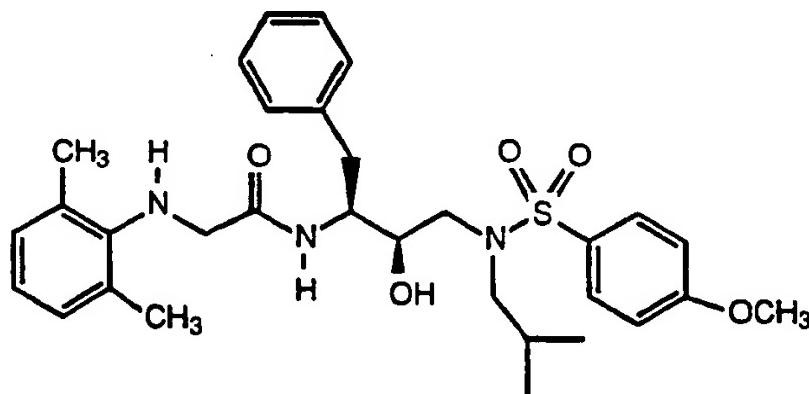
5 To a solution of 97 mg (0.59 mmol) of 2-(methylphenoxy)acetic acid in 5 mL of anhydrous methylene chloride at room temperature, was added 89.1 mg (0.55 mmol) of carbonyl diimidazole. After 15 minutes of activation, 200 mg (0.49 mmol) of 2R-hydroxy-3-[[[(2-methylpropyl)(4-

10 methoxybenzene)sulfonyl]amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 15 hours the solution was extracted with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford

15 crude product. This was chromatographed on silica gel using 25% ethyl acetate/hexane to afford 198 mg of the desired compound.

Example 10H

20



Preparation of N-[2R-hydroxy-3-[[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-(2-methylphenoxy)acetamide

25

Part A: Preparation of N-(2,6-Dimethylphenyl)glycine.

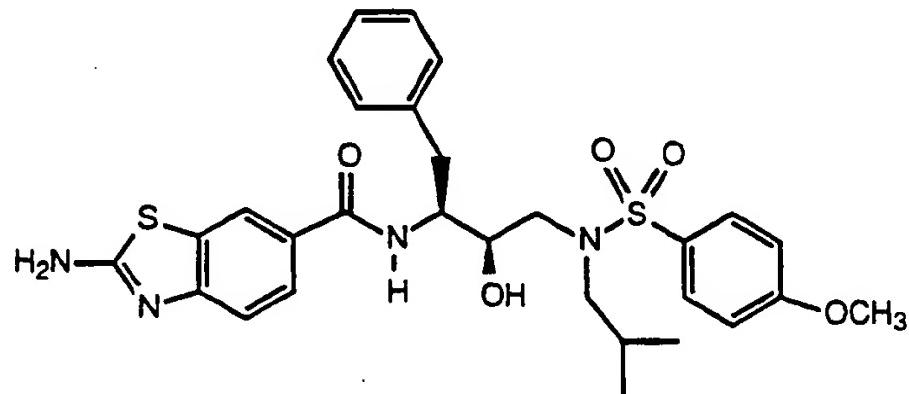
2,6-Dimethylaniline (6.1 g, 50.4 mmol), and ethyl bromoacetate (8.4 g, 50.4 mmol) were refluxed neat for 10 min. The reaction mixture was cooled to room temperature and poured into dichloromethane (75 mL). A precipitated

formed which was collected and triturated with dichloromethane (25 mL). N-(2,6-Dimethylphenyl)glycine hydrobromide salt (1.21 g, 4.6 mmol, 9.0%) was collected as a white crystalline solid. ^1H NMR (CD_3OD) δ 2.48 (s, 5 6H), 4.29 (s, 2H), 7.00-7.10 (m, 3H).

Part B: Preparation of N-[2R-hydroxy-3-[[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-(2,6-dimethylphenylamino)acetamide

To a solution of 100 mg (0.39 mmol) of N-(2,6-dimethylphenyl)glycine hydrobromide and 100 mg of triethylamine in 5 mL of anhydrous methylene chloride at room temperature, was added 74 mg (0.39 mmol) of EDC. After 15 minutes of activation, 157 mg (0.39 mmol) of 2R-hydroxy-3-[[[(2-methylpropyl)(4-methoxybenzene)sulfonyl)amino]-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 4 hours, an additional 100 mg of N-(2,6-dimethylphenyl)glycine and 74 mg of EDC was added. After stirring at room temperature for 16 hours, the solution was extracted with 5% citric acid, sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 206 mg of crude product. This was purified by chromatography on reverse phase using 20-90% acetonitrile/water (0.05% trifluoroacetic acid) to afford 75 mg of the desired compound, m/e = 568 ($\text{M}+\text{H}$).

30

Example 10I

Preparation of N-[2R-hydroxy-3-[[[4-methoxyphenyl]sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-amino-benzothiazole-6-carboxamide

5

Part A: Preparation of 2-Amino-6-Carboxy-Benzothiazole Ethyl Ester

A 100 ml round bottom flask equipped with magnetic stir bar and N₂ inlet was charged with 1.0 g of methyl p-aminobenzoate in 35 mL methanol. The solution was heated to reflux and 4.0 g of Cu^{II}SO₄ and 5.0 g of KSCN were added. The reaction mixture was refluxed 2 hours and then filtered. The filtrate was diluted with 60 mL of water and 20 mL of ethanol and heated to boiling. Upon cooling 1.15 g (78%) of 2-Amino-6-Carboxy-Benzothiazole Ethyl Ester was isolated, m/e=223 (M+H).

Part B: Preparation of 2-Amino-6-Carboxy-Benzothiazole.

20

A 50 mL round bottom flask equipped with magnetic stir bar was charged with 250 mg 2-Amino-6-Carboxy-Benzothiazole Ethyl Ester, 190 mg (4 eq.) LiOH in 3 mL dioxane and 3 mL water. The slurry was heated to 60°C for 2 hours. After 2 hours the solution was acidified with 1N HCl and concentrated in vacuo to a light grey solid which was identified as 2-amino-6-carboxy-benzothiazole, m/e = 195 (M+H). It was used without further purification.

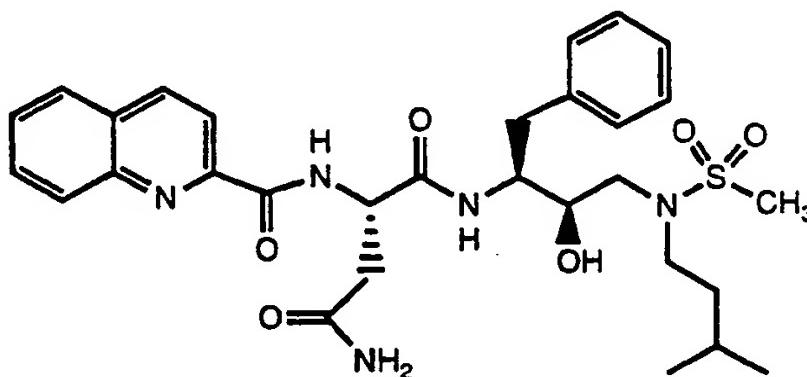
30

Part C: Preparation of N-[2R-hydroxy-3-[[[4-methoxyphenyl]sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-amino-benzothiazole-6-carboxamide

35 A 100 mL round bottom flask equipped with magnetic stir bar and N₂ inlet was charged with 110 mg 2-amino-6-carboxybenzothiazole, 110 mg EDC, and 100 mg HOBt in 4 mL dry DMF. After 30 minutes activation 203 mg amine (A)

and .5 mL of triethylamine were added and the reaction was stirred overnight. The reaction was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The combined organics were washed with 10 % aqueous Citric Acid, water, saturated aqueous sodium bicarbonate, brine and concentrated in vacuo to 210 mg white foam, identified as the desired product, m/e=589 (M+Li)

10

Example 11A

Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[2-quinolinylcarbonyl]aminobutanediamide

Part A:

A solution of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)-propyl]carbamate prepared as in Example 3 (100 mg) in methanol (10 mL) was hydrogenated over 10% palladium on carbon for 2 hours, filtered through diatomaceous earth and concentrated to give the product as an oil.

25

Part B:

A solution of N-CBZ-L-asparagine (61 mg, 0.23 mmol) and N-hydroxybenzotriazole (33 mg, 0.22 mmol) in DMF (2 mL) was cooled to 0° C with an ice bath and 30 then EDC (42 mg, 0.22 mmol) was added. The solution was stirred for 30 minutes at 0° C and then the product of Part A (69 mg, 0.21 mmol) in DMF (2 mL) was added. After

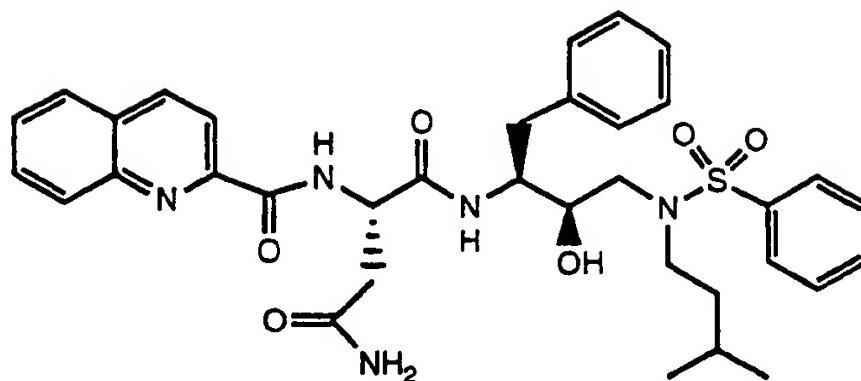
30 minutes at 0° C the reaction was allowed to warm to room temperature and stir for 16 hours. The reaction mixture was then poured into a 50% saturated aqueous solution of sodium bicarbonate (100 mL) and the resulting white precipitate collected by suction filtration, washed with water and dried *in vacuo*. The phenylmethyl [3-amino-1*S*-[(2*R*-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1*S*-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate was obtained as a white solid Anal. Calcd. for C₂₈H₄₀N₄O₇S . 0.5 H₂O: C, 57.42; H, 7.06; N, 9.57. Found: C, 57.72; H, 7.21; N, 9.24.

Part C:

A solution of phenylmethyl [3-amino-1*S*-[(2*R*-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1*S*-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate (135 mg, 0.23 mmol) in methanol (15 mL) was hydrogenated over 10% palladium on carbon for 6 hours, filtered through diatomaceous earth and concentrated to give the product as an oil.

Part D:

To a solution of the product from Part C (101 mg, 0.23 mmol) in DMF (5 mL) was added 2-quinoline carboxylic acid N-hydroxysuccinimide ester (67 mg, 0.25 mmol). The reaction was stirred at room temperature for 16 hours, then poured into a 50% saturated solution of sodium bicarbonate (60 mL). The resulting solid was collected by suction filtration washed with water and dried *in vacuo*. The N1-[2*R*-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)-amino]-1*S*-(phenylmethyl)propyl]-2*S*-[(2-quinolinylcarbonyl)-amino]butanediamide was obtained as a white solid Anal. Calcd. for C₃₀H₃₉N₅O₆S . 0.1 H₂O: C, 58.52; H, 6.71; N, 11.37. Found: C, 58.34; H, 6.35; N, 11.13.

Example 11B

5 Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)aminolbutanediamide.

Part A:

10 The CBZ protected compound phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate (200 mg, 0.38 mmol) was deprotected by hydrogenation over 10% palladium on carbon and the resulting product obtained as an oil.

15

Part B:

The free amine from Part A was coupled with N-CBZ-L-asparagine (109 mg, 0.41 mmol) in the presence of N-hydroxybenzotriazole (63 mg, 0.41 mmol) and EDC (77 mg, 0.40 mmol) to give phenylmethyl [3-amino-1S-[(2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate as a white solid. Anal. Calcd. for C₃₃H₄₂N₄O₇S: C, 62.05; H, 6.63; N, 8.77. Found: C, 61.86; H, 6.60; N, 8.64.

25

Part C:

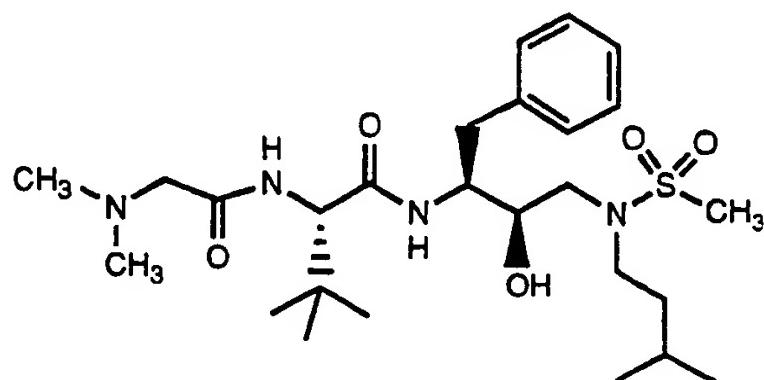
The product of Part B (110 mg, 0.17 mmol) was deprotected by hydrogenation over 10% palladium on carbon to give the product as an oil.

30

Part D:

The resulting free amine was coupled with 2-quinoline carboxylic acid N-hydroxysuccinimide ester (45 mg, 0.17 mmol) to give N1- [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide as a white solid. Anal. Calcd. for C₃₅H₄₁N₅O₆S: C, 63.71; H, 6.26; N, 10.61. Found: C, 63.59; H, 6.42; N, 10.42.

10

Example 12A

Preparation of 2S-[(dimethylamino)acetyl]aminol-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutanamide

Part A:

To a solution of N-CBZ-L-tert-leucine (100 mg, 0.38 mmol) and N-hydroxybenzotriazole (52 mg, 0.34 mmol) in DMF (3 mL) was added EDC (65 mg, 0.34 mmol). The solution was stirred for 60 minutes at room temperature and then the product of Example 10, Part A (105 mg, 0.32 mmol) in DMF (2 mL) was added. The reaction was stirred for 16 hours at room temperature, then poured into a 50% saturated solution of sodium bicarbonate (50 mL). The aqueous mixture was extracted twice with ethyl acetate (25 mL). The combined ethyl acetate layers were washed with water (25 mL) and dried over magnesium sulfate. Filtration and concentration produced an oil which was chromatographed on silica gel (50 gm) eluting with 2.5 % methanol in dichloromethane. The phenylmethyl [1S-[(2R-

hydroxy-3-[(3-methylbutyl)-(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]-carbonyl]-2,2-dimethylpropyl carbamate was obtained as a gummy solid
Anal. Calcd. for C₃₀H₄₅N₃O₆S + 2.2 H₂O: C, 58.55; H, 8.09; N, 6.83. Found: C, 58.38; H, 7.77; N, 7.10.

5

Part B:

A solution of phenylmethyl [1S-[[[2R-hydroxy-3-[(3-methylbutyl)-(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl carbamate (100 mg, 0.17 mmol) in methanol (10 mL) was hydrogenated over 10% palladium on carbon for 2 hours. The reaction was filtered through diatomaceous earth and concentrated to an oil.

15

Part C:

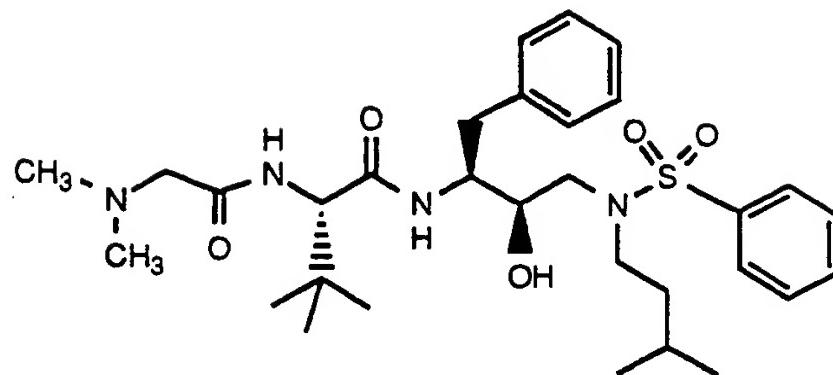
N,N-dimethylglycine (20 mg, 0.19 mmol), N-hydroxybenzotriazole (28 mg, 0.18 mmol) and EDC (35 mg, 0.18 mmol) were stirred in DMF (4 mL) at room temperature for 40 minutes. The product from Part B in DMF (4 mL) was added and the reaction mixture stirred for 16 hours, then poured into a 50% saturated sodium bicarbonate solution (50 mL). The aqueous mixture was extracted three times with dichloromethane (30 mL) which in turn were washed with water (30 mL) and dried over magnesium sulfate. Filtration and concentration afforded an oil. The oil was chromatographed on silica gel (50 gm) eluting initially with 2.5 % methanol in dichloromethane (400 mL) and then with 5% methanol in dichloromethane. The 2S-[[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)-(methylsulfonyl)amino]-1S-(phenylmethyl)-propyl]-3,3-dimethylbutanamide was obtained as a white solid
Anal. Calcd. for C₂₆H₄₆N₄O₅S + 0.5 CH₂Cl₂: C, 56.04; H, 8.34; N, 9.87. Found: C, 56.06; H, 8.36; N, 9.70.

20

25

30

35

Example 12B

5 Preparation of 2S-[[[(dimethylamino)acetyl]aminol-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]-3,3-dimethylbutaneamide

Part A:

10

To a solution of N-CBZ-L-tert-leucine (450 mg, 1.7 mmol) and N-hydroxybenzotriazole (260 mg, 1.7 mmol) in DMF (10 mL) was added EDC (307 mg, 1.6 mmol). The solution was stirred for 60 minutes at room temperature
 15 and then the product of Example 11, Part A (585 mg, 1.5 mmol) in DMF (2 mL) was added. The reaction was stirred for 16 hours at room temperature, then poured into a 50% saturated solution of sodium bicarbonate (200 mL). The aqueous mixture was extracted thrice with ethyl acetate (50 mL). The combined ethyl acetate layers were washed with water (50 mL) and saturated NaCl solution (50 mL), then dried over magnesium sulfate. Filtration and concentration produced an oil which was chromatographed on silica gel
 20 (50 gm) eluting with 20% ethyl acetate in hexane. The phenylmethyl [1S-[[[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl]carbamate was obtained as a solid Anal. Calcd for C₃₅H₄₇N₃O₆S: C, 65.91; H, 7.43; N, 6.59. Found: C, 65.42; H, 7.24; N, 6.55.

Part B:

A solution of phenylmethyl [1S-[[[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)-amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl carbamate (200 mg, 0.31 mmol) in methanol (15 mL) was hydrogenated over 10% palladium on carbon for 2 hours. The reaction was filtered through diatomaceous earth and concentrated to an oil.

10

Part C:

The resulting free amine from part B (150 mg, 0.3 mmol) was combined with diisopropylethylamine (114 uL, 0.33 mmol) in dichloromethane (5 mL). To this was added bromoacetyl chloride (27 uL, 0.33 mmol) dropwise. The reaction was stirred for 30 minutes at room temperature, then diluted with dichloromethane (30 mL) and extracted with 1 N HCl, water, and then saturated NaCl solution (25 mL each). The organic solution was dried over MgSO₄ and concentrated to a solid. The 2S-[[bromoacetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was sufficiently pure for use in the next step. This material can also be prepared by substituting bromoacetic anhydride for bromoacetyl chloride, or one can use chloroacetyl chloride or chloracetic anhydride.

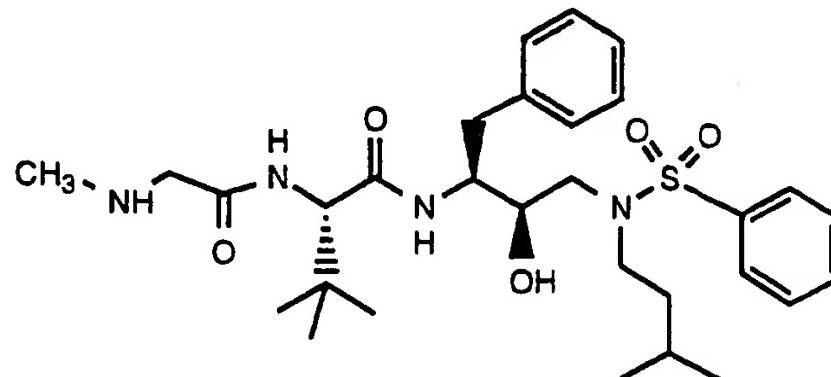
30 Part D:

The product from part C was dissolved in dichloromethane (5 mL) and diisopropylethylamine (114 uL, 0.66 mmol) and dimethylamine hydrochloride (53 mg, 0.66 mmol) were added. The reaction was stirred for 18 hours then concentrated under a stream of nitrogen to about 1 mL. The residue was chromatographed on silica gel (50 gm) using 2% methanol in dichloromethane. The

2S-[(dimethylamino)-acetyl] amino]-N-[2R-hydroxy-3-[(3methylbutyl)-(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was obtained as a solid. Anal. Calcd for C₃₁H₄₈N₄O₅S: C, 63.24; H, 8.22; N, 9.52.

5 Found: C, 63.03; H, 8.01; N, 9.40.

Example 12C



10

Preparation of 2S-[(methylamino)acetyllaminol-N-[2R-hydroxy-3-[(3-methylbutyl)-(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide

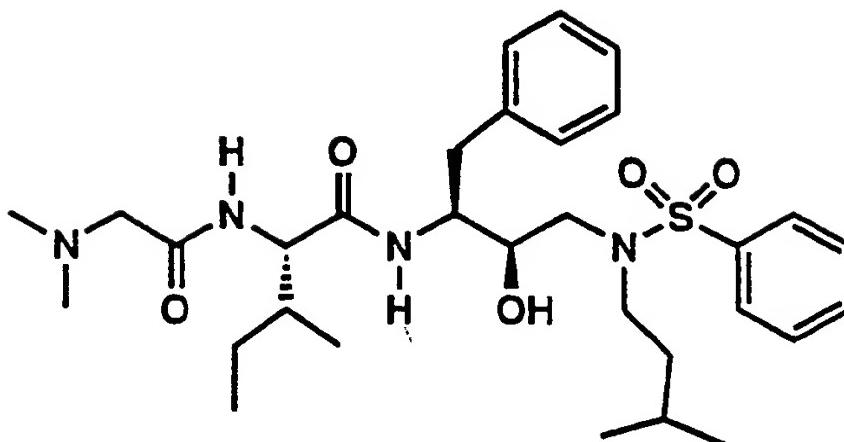
15

2S-[(bromoacetyl)amino]-N-[2R-hydroxy-3-[(3-methylbutyl)-(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide (103 mg, 0.16 mmol) and 40% aqueous methylamine (42 uL, 0.49 mmol) were combined in ethanol (2 mL) and stirred at room temperature for 24 hours. The reaction mixture was concentrated to dryness and triturated with ether. The solid material was removed by filtration and the filtrate concentrated to an oil. The oil was chromatographed on silica (50 gm) using 4% methanol in dichloromethane. The 2S-[(methylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)-(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was obtained as a solid. Anal. Calcd for C₃₀H₄₆N₄O₅S: C, 62.69; H, 8.07; N, 9.75. Found:

20 C, 62.38; H, 8.14; N, 9.60.

25

30

Example 12D

5 Preparation of Pentanamide, 2S-[[[dimethylamino]acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)phenylsulfonyl]amino]-1S-(phenylmethyl)propyl]-3S-methyl-

Part A:

10 To a solution the amine product of Example 11, Part A; (2.79 g, 7.1 mmol) in 27 mL of dioxane was added (2.3 g, 7.1 mmol) of N-t-butylcarbonyl-L-isoleucine-N-hydroxysuccinamide ester, and the reaction was stirred under nitrogen atmosphere for 16 hours. The contents of
15 the reaction were concentrated in vacuo, and the residue dissolved in ethyl acetate, washed with potassium hydrogen sulfate (5% aqueous), saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered and
20 concentrated to yield 4.3 grams of crude material which was chromatographed using 3:1 ethyl acetate: hexane to obtain 3.05g, 72% yield of Pentanamide, 2S-[[((1,1-dimethylethoxy)carbonyl)amino]-N-[2R-hydroxy-3-[(3-methylbutyl)phenylsulfonyl]amino]-1S-
25 (phenylmethyl)propyl]-3-methyl-.

Part B

(3.05g, 5.0 mmol) of the product from Part A was dissolved in 20 mL of 4N HCl in dioxane and stirred
30 under nitrogen atmosphere for 1.5 hours. The contents were concentrated in vacuo, and chased with diethyl

ether. The crude hydrochloride salt was pumped on at 1 mm Hg until dry to yield 2.54 g of product as its hydrochloride salt.

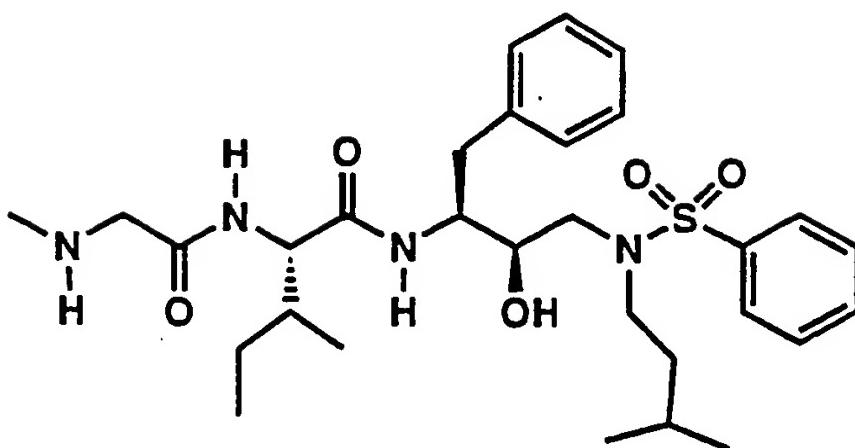
5 Part C:

(2.54 g, 5.0 mmol) of amine hydrochloride was dissolved in 50 mL of tetrahydrofuran and to this was added (1.01 g, 10 mmol) of 4-methyl-morpholine, at which time a precipitate forms. To this suspension was added 10 chloroacetic anhydride (0.865 g, 5.0 mmol) and stirred for 40 minutes. The contents were concentrated in vacuo, and the residue partitioned in ethyl acetate (200 mL) and 5% KHSO₄. The organic layer was washed with saturated sodium bicarbonate, and saturated sodium chloride, dried 15 over magnesium sulfate, filtered and concentrated to yield the crude product. Purification by silica gel chromatography using an eluant of 1:1 ethyl acetate: hexanes yielded 1.89 grams of pure chloroacetamide.

20 Part D:

To a solution of chloroacetamide (1.89 g, 3.2 mmol) from Part C, in 25 mL of tetrahydrofuran was added 4.0 mL of 50% aqueous dimethylamine and the solution was stirred for 1 hour. The solution was concentrated in 25 vacuo and the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered and concentrated to yield the crude product which was purified by crystallization from ethyl acetate and isooctane to yield 1.80 g, (88% yield), 30 mp. = 121-122 C, HRes. MS. calc. 589.3424, found 589.3405.

100

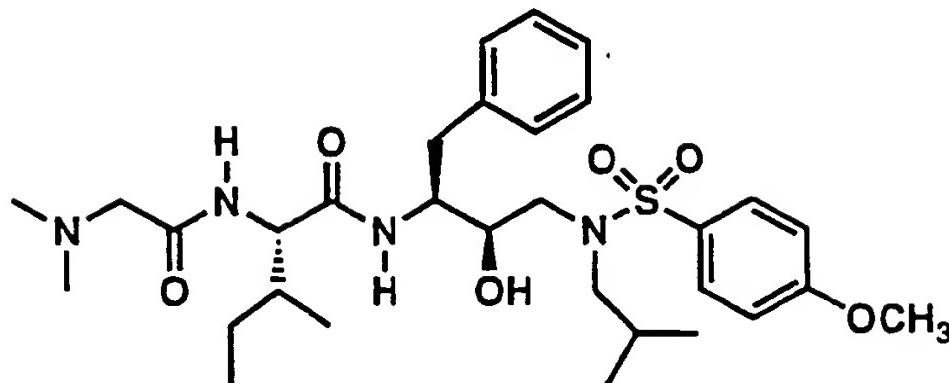
Example 12E

5 Preparation of Pentanamide, 2S-
[(Methylamino)acetyl]aminol-N-[2R-hydroxy-3-[3-
methylbutyl](phenylsulfonyl)aminol-1S-
(phenylmethyl)propyl]-3S-methyl-

10 To a solution of the chloroacetamide of Example 12D, Part C, (2.36 g, 4.0 mmol) in tetrahydrofuran (25 mL) was added 3 mL of aqueous methylamine 40 wt%, and the reaction stirred for 1 hour. The contents were concentrated and the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to yield the crude product, which was purified by recrystallization from ethyl acetate heptane; (M+H)_n 575, HRes. found 575.3267.

15

20

Example 12E

5 Preparation of Pentanamide, 2S-[(dimethylamino)acetyl]aminol-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl-

10 Part A:

To a solution of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propylamine (1.70 g, 4.18 mmol) in 40 mL of dichloromethane was added N-carbobenzyloxy-L-isoleucine-N-hydroxysuccinamide ester (1.51 g, 4.18 mmol) and the solution stirred under nitrogen atmosphere for 16 hours. The contents were concentrated in vacuo and the residue was redissolved in ethyl acetate. The ethyl acetate solution was washed with an aqueous solution of 5% KHSO₄, saturated sodium bicarbonate, and saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to yield 2.47g of crude product. The product was purified by silica gel chromatography using 1 2:1 hexane:ethyl acetate eluant to yield 2.3 g. (84% yield) of 2S-[(carbobenzyloxy)amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methylpentanamide.

Part B:

30 (1.18 g, 1.8 mmol) of the product from Part A was dissolved in 50 mL of methanol, and to this was added 250 mg of 10% Palladium on Carbon while under a stream of

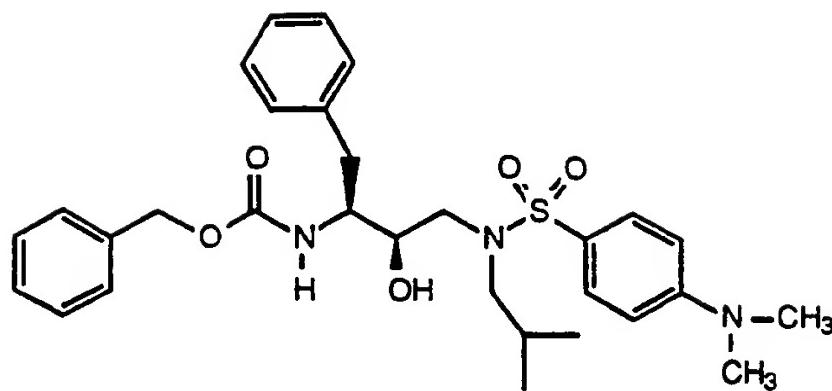
nitrogen. The suspension was hydrogenated using 50 psig of hydrogen for 20 hours. The contents were purged with nitrogen and filtered through celite, and concentrated in vacuo to yield 935 mg of 2S-(amino)-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl) amino]-1S-(phenylmethyl)propyl]-3S-methylpentanamide, which was used without further purification.

Part C:

(0.935 g, 1.8 mmol) of the amine from Part B was dissolved in 15 mL of dioxane and to this was added (190 mg, 1.85 mmol) of 4-methylmorpholine followed by (0.315 g, 1.8 mmol) of chloroacetic anhydride. The reaction mixture was stirred under nitrogen atmosphere for 3 hours, concentrated in vacuo, and redissolved in ethyl acetate. The ethyl acetate solution was washed with 50 mL of 5% aqueous KHSO₄, saturated NaHCO₃, and saturated NaCl solution, dried over MgSO₄, filtered and concentrated to yield 613 mg, (68% yield) of 2S-[(chloroacetyl)amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methylpentanamide, after purification by silica gel chromatography using 1:1 hexane:ethyl acetate.

25 Part D:

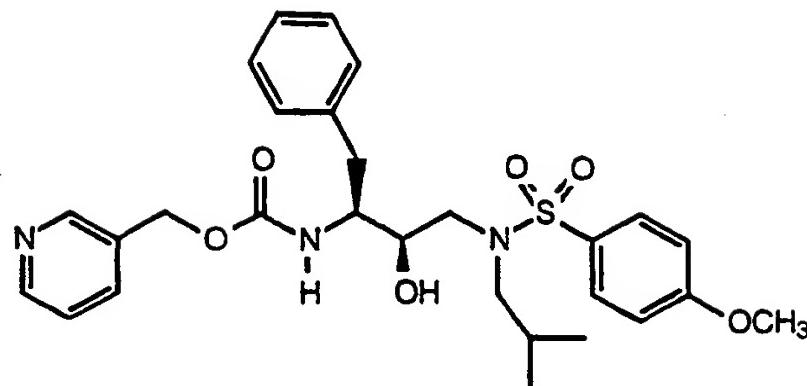
To a solution of the chloroacetamide from Part C (673 mg, 1.10 mmol) in 20 mL of tetrahydrofuran was added 5 mL of 50 wt% aqueous dimethylamine and the solution was stirred for 1 hour. The reaction was concentrated and the residue was redissolved in 50 mL of ethyl acetate and washed with 25 mL of water. The ethyl acetate layer was dried over magnesium sulfate, filtered and concentrated to yield a crude solid which was purified by silica gel column chromatography using an eluant of 97:3 dichloromethane:methanol to provide 400 mg of Pentanamide, 2S-[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl-

Example 13A

5

Preparation of Carbamic acid, [2R-hydroxy-3-[[[(4-dimethylaminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester

10 To a solution of 100mg (0.19 mmol) of carbamic acid, [2R-hydroxy-3-[[[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester in 1 mL of pyridine was added 53 μ L of triethylamine and 120 μ L (p.95 mmol) of 40% aqueous
15 dimethylamine. After heating for 24 hours at 100°C, the solution was cooled, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated. The resulting solid was recrystallized from ethyl acetate/hexane to afford 10 mg of the desired product;
20 mass spectrum m/e = 540 (M+H).

Example 13B

- 5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester

Part A:

10 A solution of N-benzyloxycarbonyl-3S-amino-1,2-S-epoxy-4-phenylbutane (50g, 0.168 mol) and isobutylamine (246g, 3.24 mol) in 650 mL of isopropyl alcohol was refluxed for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 15 1L of stirring hexane whereupon the product crystallized from solution, was collected and air dried to give 57.6 g of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine, mp 108-109.5°C, mass spectrum m/e=371 (M+H).

20

Part B:

The amine from part A (1.11g, 3.0 mmol) and triethylamine (324mg, 3.20 mmol) in 20 mL of methylene chloride was treated with 715 mg (3.46 mmol) of 4-methoxybenzenesulfonyl chloride. The solution was stirred at room temperature for 6 hours, concentrated, dissolved in ethyl acetate, then washed with 1N potassium hydrogen sulfate, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated 25 to afford a clear oil. This was recrystallized from diethyl ether to afford 1.27 g of carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)

amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, mp 97-101°C, mass spectrum m/e=541 (M+H).

Part C:

5 A solution of 930mg (3.20 mmol) of the product of part B in 30 mL of methanol was hydrogenated in the presence of 70 mg of a 10% palladium on carbon catalyst under 40 psig for 17 hours, the catalyst was removed by filtration, and the solution concentrated to afford 704
10 mg of [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine, mass spectrum m/e = 407 (M+H), which was used directly in the next step without purification.

15 Part D:

To a solution of 2.5g (22.9 mmol) of 3-pyridylcarbinol in 100 mL of anhydrous acetonitrile was added 8.8 g (34.4 mmol) of N,N'-disuccinimidyl carbonate and 5.55 mL (68.7 mmol) of pyridine. The solution was
20 stirred for 1 hour and then concentrated in vacuo. The residue was dissolved in ethyl acetate, then washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 5.3 g of N-Hydroxysuccinimide-3-pyridylmethyl carbonate, mass
25 spectrum m/e = 251 (M+H), which was used directly in the next step without purification.

Part E:

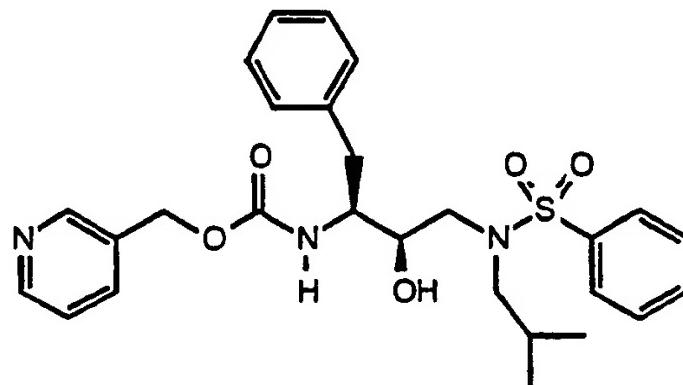
To a solution of the amine from part C (2.87g,
30 7.0 mmol) and 1.38 mL of triethylamine in 24 mL of anhydrous methylene chloride was added a solution of 1.65g (6.6 mmol) of N-hydroxysuccinimide-3-pyridyl carbonate from part D in 24 mL of methylene chloride. The solution was stirred for 1 hour, 100 mL of methylene chloride
35 added, then washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated to afford 3.69 g of crude product.
Chromatography on silica gel using 2% methanol/methylene

106

chloride to afford 3.27 g of carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-pyridylmethyl ester, mass spectrum m/e = 548 (M+Li).

5

Example 13C



10 Preparation of Carbamic acid, [2R-hydroxy-3-1-(phenylsulfonyl)(2-methylpropyl)aminol-1S-(phenylmethyl)propyl-, 3-pyridylmethyl ester

Part A:

15 A solution of N-benzyloxycarbonyl-3S-amino-1,2-S-epoxy-4-phenylbutane (50g, 0.168 mol) and isobutylamine (246g, 3.24 mol) in 650 mL of isopropyl alcohol was refluxed for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into
20 1L of stirring hexane whereupon the product crystallized from solution, was collected and air dried to give 57.6 g of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine, mp 108-109.5 C, mass spectrum m/e=371 (M+H).
25

Part B:

The amine from part A (0.94g, 2.5 mmol) and triethylamine (288 mg, 2.85 mmol) in 20 mL of methylene chloride was treated with 461 mg (2.61 mmol) of
30 benzenesulfonyl chloride. The solution was stirred at room temperature for 16 hours, concentrated, dissolved in ethyl acetate, then washed with 1N potassium hydrogen

sulfate, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford a clear oil. This was recrystallized from diethyl ether and hexane to afford 0.73 g of carbamic acid, [2R-
5 hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, mp 95-99 C, mass spectrum m/e=511 (M+H).

Part C:

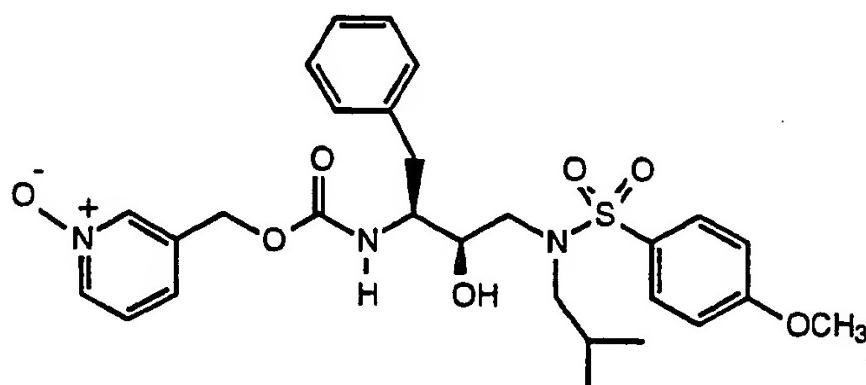
10 A solution of 500mg of carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester in 20 mL of methanol was hydrogenated in the presence of 250 mg of a 10% palladium on carbon catalyst under 40 psig for 3
15 hours, the catalyst was removed by filtration, and the solution concentrated to afford 352 mg of [2R-hydroxy-3-[(phenylsulfonyl)]2-methylpropyl)amino]-1S-(phenylmethyl)propylamine, mass spectrum m/e = 377 (M+H), which was used directly in the next step without
20 purification.

Part D:

To a solution of 1.24 mmol of 5-norbornene-2,3-dicarboximido carbonochloridate (Henklein, P., et. al.,
25 Synthesis 1987, 166-167) in 1 mL of anhydrous methylene chloride, was added a solution of 43 μ L (2.44 mmol) of 3-pyridylcarbinol and 129 μ L (1.6 mmol) of pyridine in 1 mL of methylene chloride at 0°C under a nitrogen atmosphere. After 4 hours at room temperature, 150 mg (0.4 mmol) of
30 [2R-hydroxy-3-[(phenylsulfonyl)]2-methylpropyl)amino]-1S-(phenylmethyl)propylamine from Part C above was added and 100 μ L of pyridine. After stirring for 15 hours at room temperature, ethyl acetate was added, then washed with 1N hydrochloric acid, saturated sodium bicarbonate, brine,
35 dried over magnesium sulfate, filtered and concentrated to afford 175 mg of crude product. Chromatography over silica gel using 1% methanol/methylene chloride to afford 69 mg of pure carbamic acid, [2R-hydroxy-3-

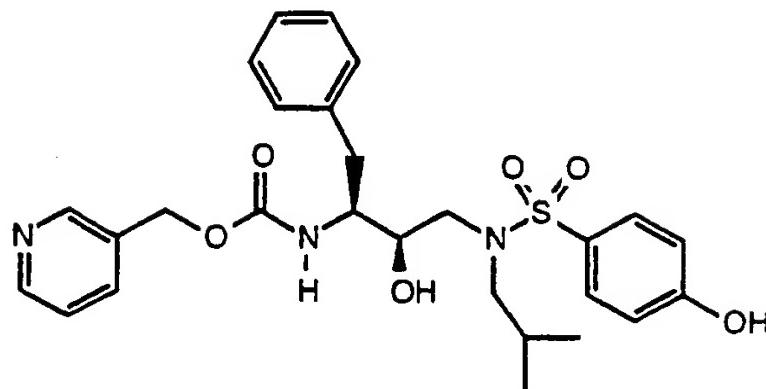
[(phenylsulfonyl) (2-methylpropyl)amino]-1S-(phenylmethyl) propyl] -, 3-pyridylmethyl ester, mass spectrum m/e = 512.2267 (M+H); calcd for C₂₇H₃₃N₃O₅S, 512.2219.

5

Example 13D

Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
10 methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide

To a solution of 211mg (0.39 mmol) of carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-
15 methylpropyl)amino]-1S-(phenylmethyl)propyl] -, 3-
pyridylmethyl ester in 5mL of methylene chloride at 0°C
was added 500 mg of 50% 3-chloroperbenzoic acid. After
stirring at room temperature for 1 hour, ethyl acetate
was added, the solution washed with saturated sodium
20 bicarbonate, 0.2N ammonium hydroxide solution and brine,
dried over magnesium sulfate, filtered and concentrated
to afford 200 mg of crude product. This was
chromatographed on C18 reverse phase material using 20-
40% acetonitrile/water, then 100% acetonitrile to afford
25 90mg of the desired product, which was then
recrystallized from ethyl acetate/isooctane to yield 34mg
of pure carbamic acid, [2R-hydroxy-3-[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide;
30 mass spectrum m/e=564 (M+Li).

Example 13E

5 Preparation of Carbamic acid, [2R-hydroxy-3-[[4-hydroxyphenyl]sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl]-3-pyridylmethyl ester

Part A:

10 A solution of 0.98 g (1.85 mmol) of carbamic acid, [2R-hydroxy-3-[[4-fluorophenyl]sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-phenylmethyl ester in 3.8 mL of anhydrous DMF was added to 22mg (7.4 mmol) of 80% sodium hydride in 2 mL of DMF. To this
15 mixture was added 0.40g (3.7 mmol) of benzyl alcohol. After 2 hours, the solution was cooled to 0 C, water added, and then ethyl acetate. The organic layer was washed with 5% cirtic acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and
20 concentrated to afford 0.90g of crude material. This was chromatographed on basic alumina using 3% methanol/methylene chloride to afford 0.70g of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine, cyclic carbamate;
25 mass spectrum m/e=509 (M+H).

Part B:

To a solution of 0.65g (1.28 mmol) of the cyclic carbamate from part A in 15 mL of ethanol, was added 2.6 mL (6.4 mmol) of 2.5N sodium hydroxide solution. After 1 hour at reflux, 4 mL of water was added and the solution refluxed for an additional eight hours. The volatiles were removed, ethyl acetate added, and washed with water, brine, dried over magnesium sulfate, filtered and concentrated to afford 550 mg of crude 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine.

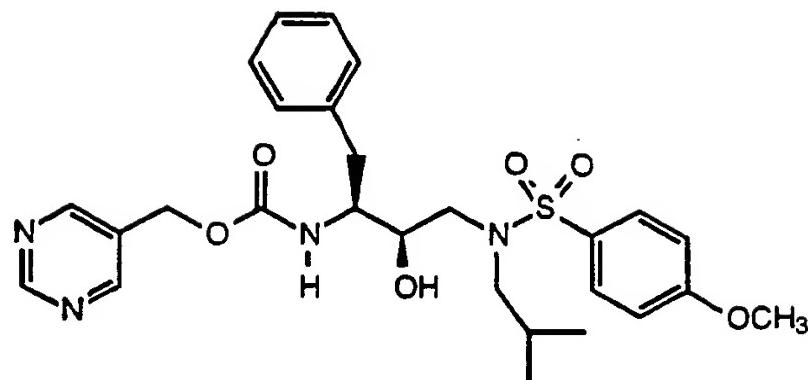
Part C:

A solution of crude 2R-hydroxy-3-[(2-methylpropyl)(4-benzyloxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 10 mL of ethanol was hydrogenated in the presence of 500 mg of a 10% palladium on carbon catalyst under 50 psig of hydrogen for 2 hours. The catalyst was removed by filtration and the solvent removed in vacuo to afford 330 mg of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine, mass spectrum m/e = 393 (M+H).

Part D:

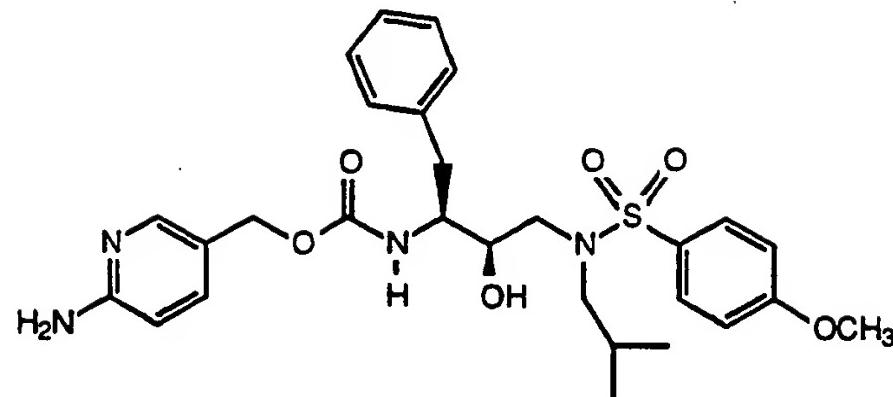
To a solution of 320 mg (0.82 mmol) of the amine from part C in 6 mL of DMF, was added 192 mg (0.76 mmol) of N-hydroxysuccinimide-3-pyridylmethyl carbonate. After 15 hours at room temperature, the DMF was removed in vacuo, ethyl acetate added, washed with water, brine, dried with magnesium sulfate, filtered and concentrated to afford 390 mg of crude material. Chromatography on silica gel using 50-80% ethyl acetate/hexane afforded 180 mg of carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, mass spectrum m/e = 528 (M+H).

111

Example 13E

5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)aminol-1S-
(phenylmethyl)propyl-, 5-pyrimidylmethyl ester

To a solution of 9.5mg (0.09mmol) of 5-pyrimidylcarbinol in 1mL of anhydrous acetonitrile at room temperature, was added 24mg (0.09mmol) of N,N'-disuccinimidyl carbonate and 19.1 μ L (0.24mmol) of pyridine. After stirring for 5 hours, 32 mg (0.08mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added and the solution stirred for 48 hours. After concentration in vacuo, methylene chloride was added, then washed with a 1:1 mixture of saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to give 27 mg of crude product. Chromatography on silica gel using 2% methanol/methylene chloride afforded 22 mg of the desired product, mass spectrum m/e=543 (M+H).

Example 13G

- 5 Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](2-methylpropyl)aminol-1S-
(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester.

Part A: Preparation of Ethyl 6-Aminonicotinate

10

To a suspension of 1.3g (9.4 mmol) 6-aminonicotinic acid in 100 mL of ethanol, was bubbled in dry hydrochloric acid at 0°C, then the solution was refluxed until all the solids dissolved. The solvents were removed under reduced

15 pressure, the residue dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine and concentrated to afford 1.37g of a white solid, m/e=166(M+H).

Part B: Preparation of Ethyl 6-(tert-
20 Butyloxycarbonylamino)nicotinate

A mixture of 848 mg(5.1 mmol) of ethyl 6-aminonicotinate from part A, 1.11g(5.1 mmol) of di-tert-butylpyrocarbonate and 0.71 mL (5.1 mmol) of triethylamine in 10mL of anhydrous 25 toluene was refluxed for 15 hours. The solution was cooled, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.28g of the desired ethyl 6-(tert-butyloxycarbonylamino)nicotinate, m/e=267(M+H), which was used directly in the next step.

Part C: Preparation of 6-(tert-Butyloxycarbonylamino)-3-pyridylmethanol

To 4.6 mL (4.6 mmol) of a 1M solution of lithium aluminum hydride in diethyl ether at -40°C under a nitrogen atmosphere, was added a slution of 618mg (2.3 mmol) of ethyl 6-(tert-butyloxycarbonylamino)nicotinate from part B in 40 mL of anhydrous tetrahydrofuran. After the addition, this was warmed to room temperature, stirred for 3 hours, cooled to 0°C, and 145 µL of water, 145µL of 20% sodium hydroxide solution and 290µL of water were successively added. To the resulting mixture was added 50mL of tetrahydrofuran and stirring continued for 30 minutes. Anhydrous magnesium sulfate was added, the solids removed via filtration and the filtrate concentrated under reduced pressure to afford 460 mg of the desired product, m/e=224 (M+), which was used directly in the next step.

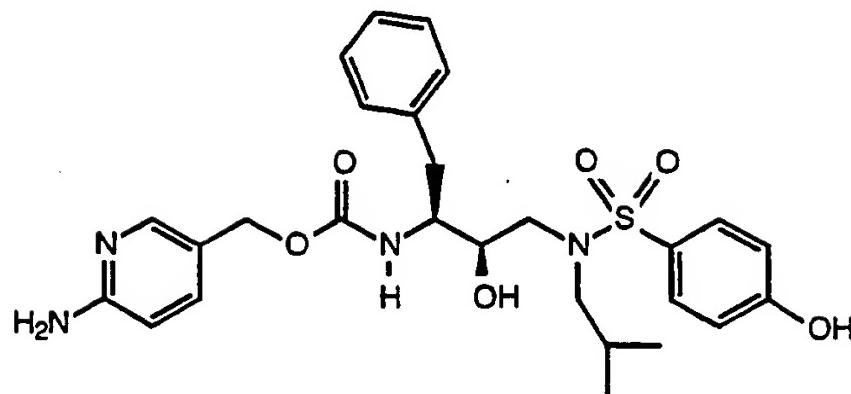
Part D: Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester

To a solution of 336 mg (1.5mmol) of 6-(tert-butyloxycarbonylamino)-3-pyridylmethanol from part C in 14 mL of anhydrous acetonitrile at room temperature under a nitrogen atmosphere, was added 384 mg(1.5mmol) of N,N'-disuccinimidyl carbonate and 364 µL (4.5mmol) of anhydrous pyridine. After 4 hours, 406mg (1mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added and stirring continued for 19 hours. The solvent was removed under reduced pressure, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 702 mg of crude product. Chromatography on silica gel using 1% methanol/methylene chloride as eluent afforded 170 mg of the desired carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-

methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester, m/e=663 (M+Li).

Part E: Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester

To 5mL of 4N hydrochloric acid in dioxane at room temperature, was added 150mg (0.23mmol) of carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester from part D. After stirring at room temperature for 28 hours, the solvent was removed under reduced pressure, the resulting solids triturated with diethyl ether, then dissolved in ethyl acetate and saturated sodium bicarbonate slution, separated, the organic layer washed with brine, dried with magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel using 2.5% methanol/methylene chloride to yield 59mg of the desired carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-aminopyridyl)methyl ester, m/e=557 (M+H).

Example 13H

5 Preparation of Carbamic acid, [2R-hydroxy-3-[[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-aminopyridyl)methyl ester.

Part A: Preparation of Carbamic acid, [2R-hydroxy-3-[[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester

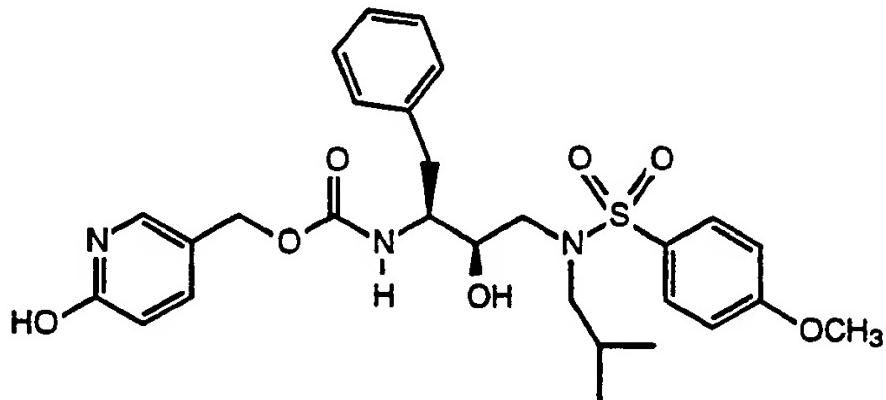
To a solution of 505 mg (2.25mmol) of 6-(tert-butyloxycarbonylamino)-3-pyridylmethanol from in 20 mL of anhydrous acetonitrile at room temperature under a nitrogen atmosphere, was added 576 mg (2.25mmol) of N,N'-disuccinimidyl carbonate and 546 μ L (6.75mmol) of anhydrous pyridine. After 1 hour, 837mg (1.87mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added and stirring continued for 3 hours. The solvent was removed under reduced pressure, ethyl acetate added, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 1.37g of crude product. Chromatography on silica gel using 1% methanol/methylene chloride as eluent afforded 830 mg of material which was identified as a mixture of the desired carbamic acid, [2R-hydroxy-3-[[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-[(6-tert-butyloxycarbonylamino)pyridyl]methyl ester and the cyclic carbamate derived from the 2R-hydroxy-3-[(2-methylpropyl)(4-

hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine. The mixture was very difficult to separate, so was used as is in the next step.

- 5 Part B: Preparation of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-(6-aminopyridyl)methyl ester

To 830mg of the mixture from part A, was added 50mL of a 1:1
10 mixture of trifluoroacetic acid and methylene chloride. After 2.5 hours at room temperature, the solvent was removed under reduced pressure, ethyl acetate added, washed with saturated sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated to afford 720 mg of crude
15 material. This was chromatographed on silica gel using 5% methanol/ethyl acetate as eluent to yield 220mg of product, which was recrystallized from methylene chloride/diethyl ether to afford 108mg of the desired carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)
20 amino]-1S-(phenylmethyl)propyl-, 3-(6-aminopyridyl)methyl ester, m/e=549 (M+Li).

Example 13I



25.

Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-(6-hydroxypyridyl)methyl ester.

30

Part A: Preparation of tert-Butyldimethylsilyl 6-(tert-butyldimethylsiloxy)nicotinate

To a solution of 5.0g (35.9mmol) of 6-hydroxynicotinic acid in 200mL of anhydrous N,N-dimethylformamide at room temperature, was added 8.56g (125mmol) of imidazole and then 13.5g (89mmol) of tert-butyldimethylsilyl chloride. After 20 hours, the solvent was removed under reduced pressure, ethyl acetate added, washed with water, 5% citric acid, saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 10.5 g of crude material, m/e=368 (M+H).

Part B: Preparation of 3-(6-tert-butyldimethylsiloxy) pyridylcarbinol

To 11mL of 1M solution of lithium aluminum hydride in diethyl ether at -35°C under a nitrogen atmosphere, was added a solution of 2.0g (5.46mmol) of product from part A in 20mL of anhydrous diethyl ether. After 30 minutes, the reaction was warmed to 0°C and stirred for 40 minutes. The solution was then quenched by the careful addition of 0.42mL of water, 0.42mL of 20% sodium hydroxide solution, and 0.84mL of ater. Ethyl acetate was added, the precipitate filtered and the organic phase concentrated to yield 0.93 g of crude 3-(6-tert-butyldimethylsiloxy)pyridylcarbinol, which was used directly in the next step.

Part C: Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester

To a solution of 860mg (3.6mmol) of material from part B in 15mL of anhydrous acetonitrile, was added 919mg (3.6mmol) of N,N'-disuccinimidyl carbonate and 0.87mL of pyridine. After 1 hour, 1.42g(3.5mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 14 hours at room temperature, the solvent was removed under reduced pressure, the residue dissolved in ethyl acetate, washed with 5% citric acid, saturated sodium

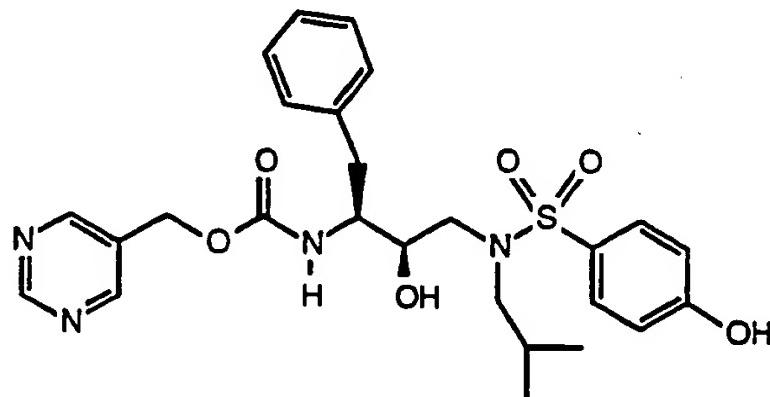
bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 2.1 g of crude material. This was directly deprotected by dissolving in 40mL of 80% acetic acid/water and stirring for 2 hours. The solvents were

5 removed under reduced pressure, the residue dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 1.7g of crude product. This was chromatographed on silica gel using 50-100% ethyl

10 acetate/hexane to provide a fraction of 0.19g of fairly pure material, which was further purified by reverse phase chromatography using 15-40% acetonitrile/water (0.05% trifluoroacetic acid) to provide 120mg of the desired

15 carbamic acid, [2R-hydroxy-3-[[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-(6-hydroxypyridyl)methyl ester, m/e=558 (M+H).

Example 13J



20

Preparation of Carbamic acid, [2R-hydroxy-3-[[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 5-pyrimidylmethyl ester.

25

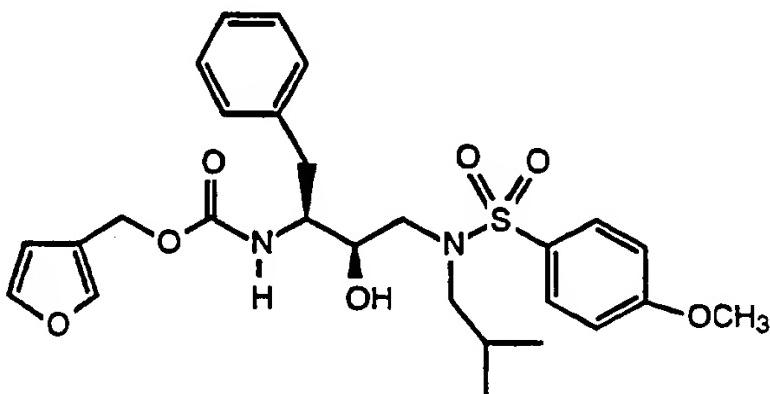
To a solution of 237mg (2.15mmol) of 5-pyrimidylcarbinol in 24mL of anhydrous acetonitrile , was added 602mg (2.35mmol) of N,N'-disuccinimidyl carbonate and then 0.47mL of pyridine. After stirring for 4.5 hours, 766mg (1.96mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring for 19 hours, the solvent was

removed under reduced pressure, ethyl acetate added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.0 g of crude material.

- 5 Chromatography on silica gel using 50-100% ethyl acetate/hexane as eluent afforded 450 mg of the desired carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 5-pyrimidylmethyl ester, m/e=529 (M+H).

10

Example 13K



- 15 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-furanyl methyl ester

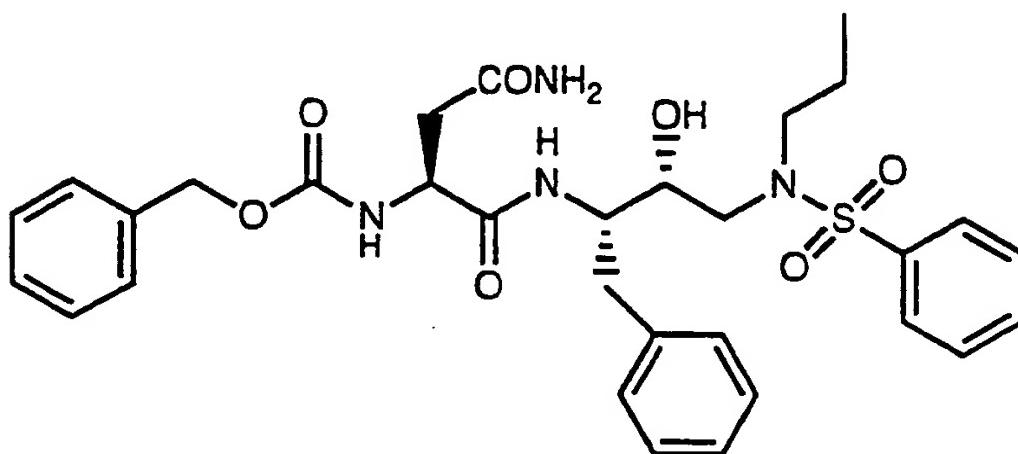
To a solution of 98mg (1 mmol) of 3-(hydroxymethyl)furan in 3 mL of anhydrous acetonitrile, was added 242 μ L of pyridine and then 256 mg of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 406 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 16 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 565 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane as eluent to afford 305mg of a white foam, which was recrystallized from diethyl ether/hexane to yield 245 mg of pure

120

carbamic acid, [2R-hydroxy-3-[[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-furanylmethyl ester, m/e = 537 (M+Li).

5

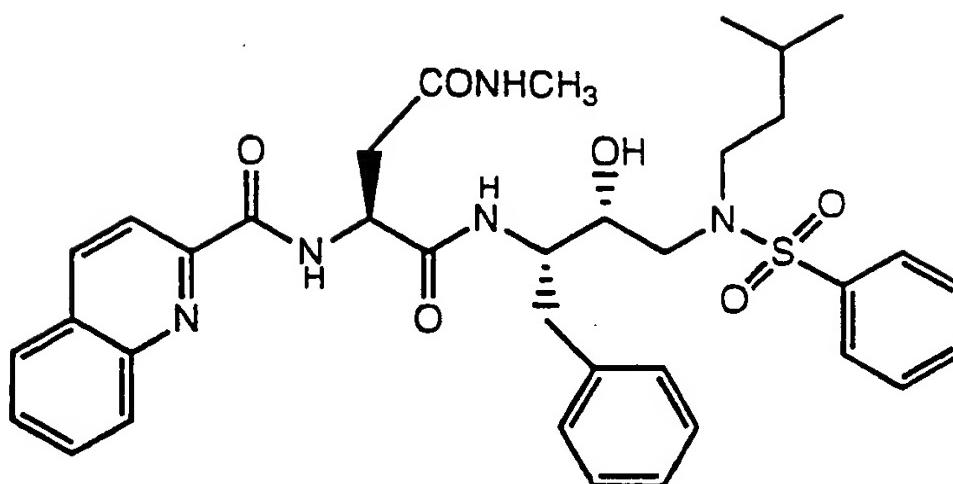
Example 14



- 10 Preparation of phenylmethyl[3-amino-1S-[2R-hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate

15 Phenylmethyl [2R-hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate (200 mg, 0.40 mmol) was deprotected by hydrogenation over 10% palladium on carbon and the resulting free amine was coupled with N-CBZ-L-asparagine (157 mg, 0.42 mmol) in the presence of N-hydroxybenzotriazole (114 mg, 0.84 mmol) and EDC (130 mg, 0.67 mmol) to give phenylmethyl[3-amino-1S-[2R-hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate as a solid. Anal. Calcd for C₃₁H₃₈N₄O₇S·0.2H₂O: C, 60.61; H, 6.30; N, 9.12. Found: C, 60.27; H, 6.16; N, 8.93.

25

Example 15A

- 5 Preparation of N¹-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N⁴-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)aminobutanediamide

Part A:

10 N²-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-asparagine was prepared from Boc-L-aspartic acid alpha-benzyl ester (1.0 g, 3.09mmol), methylamine.HCl (209 mg, 3.09mmol), EDC (711 mg, 3.7 mmol), 1-hydroxybenzotriazole (627 mg, 4.63 mmol), and N-methylmorpholine (0.7 mL, 6.3 mmol), in DMF (20mL). After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, 5% citric acid, brine, dried over magnesium sulfate and concentrated to an oil. The oil was taken up in 20 mL dry ethanol, and hydrogenated in the presence of 10% w/w of 10% Pd on C at atmospheric pressure and room temperature overnight. The mixture was filtered through Celite and concentrated to a white solid foam, 670 mg.

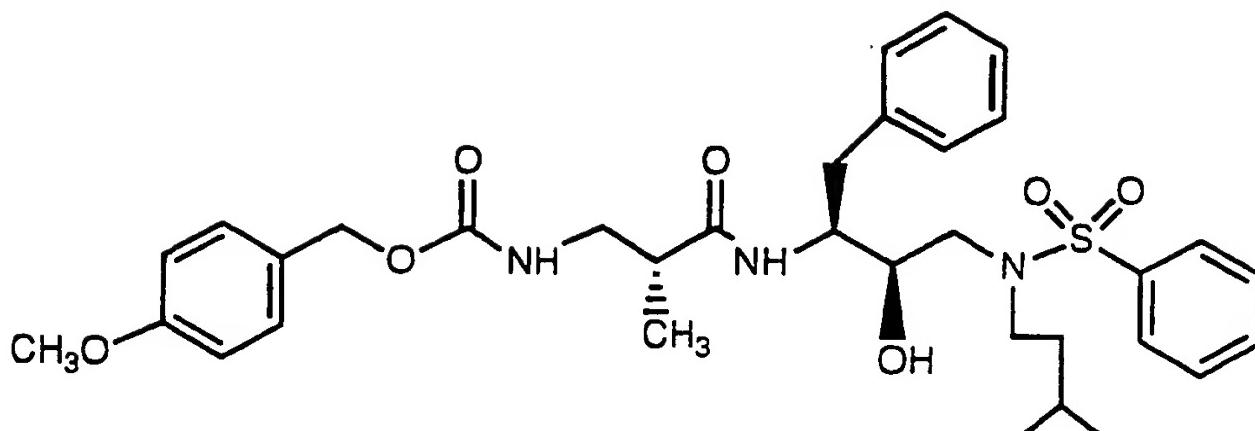
Part B:

25 A solution of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)-propyl]carbamate (310 mg, 0.59 mmol) in methanol (10mL) was hydrogenated over 10% palladium on carbon for 3 h., 30 filtered through diatomaceous earth and concentrated to

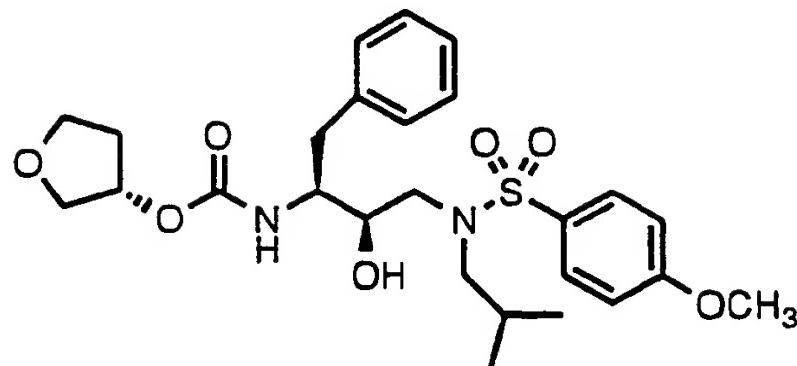
give the product as an oil (214 mg). This free amine (208 mg, 0.53 mmol) was coupled with N2-[(1,1-dimethylethoxy)-carbonyl]-N-methyl-L-asparagine (137 mg, 0.56 mmol) in the presence of N-hydroxybenzotriazole (102 mg, 0.76mmol) and EDC (130 mg, 0.67mmol) to yield 290 mg of N1[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)-amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethylethoxy-carbonyl)amino]butane diamide.

10 Part C:

N¹[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N⁴-methyl-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethylethoxycarbonyl)-amino]butane diamide (270 mg, 0.43 mmol) was stirred in 4N HCl in dioxane (5 mL) at 15 room temperature for 0.5 hr. Solvent and excess reagent were evaporated to dryness. The product was dried in vacuo. This material (125 mg, 0.225 mmol) was then reacted with 2-quinolinecarboxylic acid N-hydroxysuccimide ester (61 mg, 0.225 mmol), 20 N-methylmorpholine (50 uL, 0.45 mmol) in methylene chloride (2 mL) for 3 h. The product N¹[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N⁴-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)-amino]butanediamide was purified by silica gel 25 chromatography. Anal. Calcd for C₃₆H₄₃N₅O₆S.0.2H₂O: C, 63.83; H, 6.45; N, 10.34. Found: C, 63.64; H, 6.40; N, 10.34.

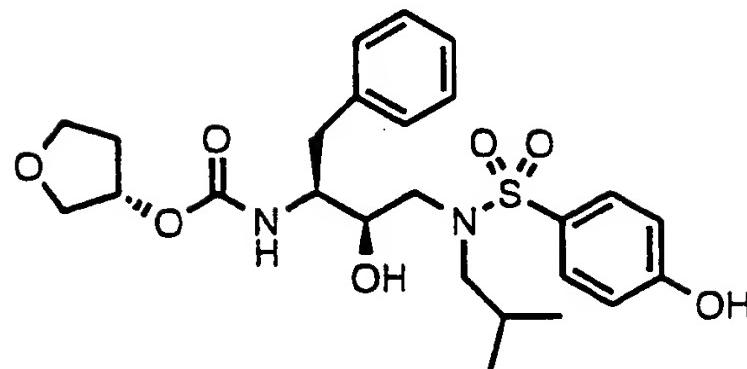
Example 15B

- 5 Preparation of Carbamic acid, [3-[2-hydroxy-3-[1-(3-methylbutyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propylaminol-2-methyl-3-oxopropyl]-, (4-methoxyphenyl)methyl ester, [1S-[1R*(S*),2S*]-
- 10 Carbamic acid, [2R-hydroxy-3-[(3-methylbutyl)(phenylsulphonyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester (4.10g, 7.8 mmol) was hydrogenated in a solution of methanol and ethanol using catalytic Pd/C 10% at 50 psig hydrogen for 3 hours. The catalyst was
- 15 filtered and the solvents removed in vacuo to yield 3.0 grams of free amine. In a separate flask, 2.09g, (7.8 mmol), of N-Moz-AMBA was added to 10 mL of dimethylformamide and 1.58g, (1.5 equiv.), of N-hydroxybenzotriazole and the solution was cooled to 5°C.
- 20 To this solution was added 1.49g, (7.8 mmol), of EDC and the solution stirred for 30 min. To this was added the free amine in 10 mL of dimethylformamide, and the reaction was stirred for 20 hours. The solvent was removed by evaporation and the crude material was
- 25 partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The ethyl acetate layer was washed with 5% potassium hydrogen sulfate and brine, dried over magnesium sulfate, filtered and concentrated to yield 2.58 grams (52%) of pure product after recrystallization
- 30 from ethyl acetate, ether, and hexanes.

Example 16A

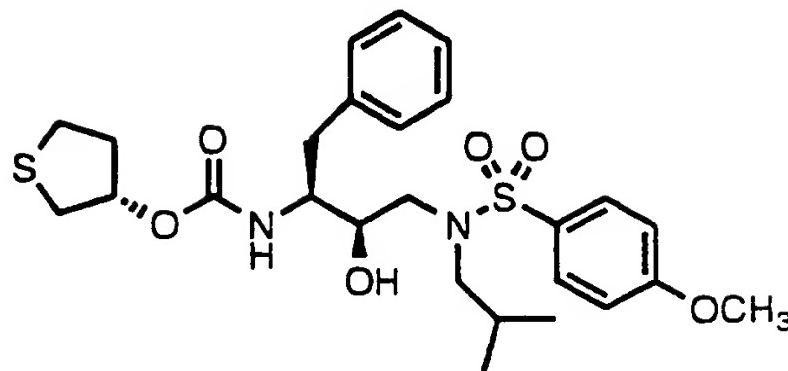
5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester,

To a solution of 406 mg (1.0 mmol) of [2R-hydroxy-3-[(4-
10 methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propylamine in 5.0 mL of dichloromethane
containing 150 mg (1.5mmol) of triethylamine was added
280mg (1.22 mmol) of N-succinimidyl-3S-tetrahydrofuranyl
carbonate and the reacton mixture was stirred for 2
15 hours, an additonal 136 mg (0.3mmol) of amine was added
to the mixture and the solution stirred another 2 hours.
The contents were diluted with 50 mL of ethyl acetate and
washed with 5% aqueous citric acid, saturated sodium
bicarbonate, and brine, then dried over magnesium
20 sulfate, filtered and concentrated to yield 330 mg of
crude product. Purification by silica gel chromatography
using an eluant of 1:1 to 2:1 ethyl acetate/hexanes
gradient provided Carbamic acid, [2R-hydroxy-3-[(4-
methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-
25 (phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester as a
white solid. m/z = 521 (M+H) calc. 521.2311 obs.
521.2311.

Example 16B

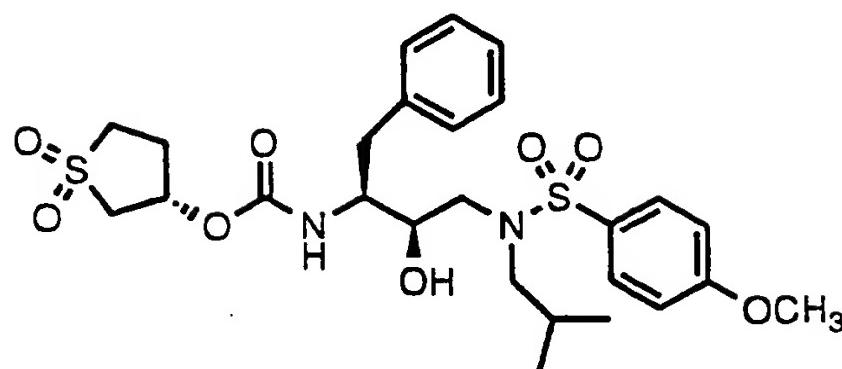
5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-
hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester,

To a solution of 435 mg (1.0 mmol) of [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propylamine in 3.0 mL of dimethylformamide was added 225mg (0.98 mmol) of N-succinimidyl-3S-tetrahydrofuranylcarbonate and the solution was stirred overnight. The mixture was diluted with 50 mL of ethyl acetate and washed with 5% aqueous citric acid, saturated sodium bicarbonate, and brine, dried over magnesium sulfate, filtered and concentrated to yield 515 mg of crude product. Purification by silica gel chromatography using and eluant of 1:1 ethyl acetate: hexanes provided 315 mg of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrofuran-3S-yl ester, as a white solid. HRMS calc. 507.2165, obs. 507.2155.

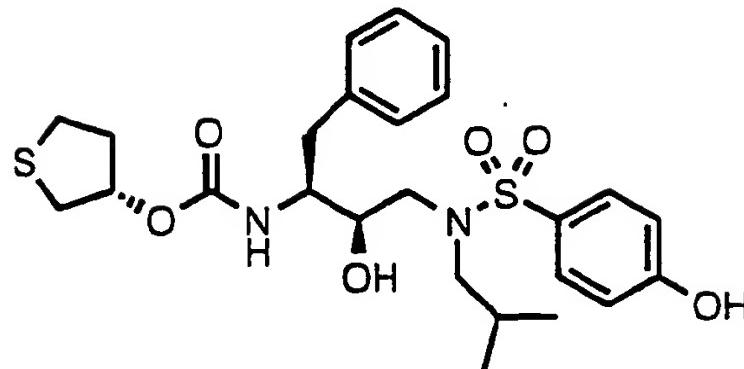
Example 16C

5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester.

To a solution of 215 mg (2.0mmol) of 3S-hydroxythiophene,
 10 415 μ L of anhydrous pyridine, and 2 mL of dry acetonitrile
 was added 512 mg (2.0 mmol) of N,N'-Dimethylsuccinimidyl
 carbonate and this suspension was stirred for 45 minutes.
 To this clear solution was added a solution of 700 mg
 (1.7 mmol) of [2R-hydroxy- 3-[(4-methoxyphenyl)
 15 sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
 propylamine in 2.0 mL of acetonitrile and stirred for 12
 hours. The contents were concentrated, and the residue
 was partitioned between ethyl acetate and 5% aqueous
 potassium hydrogen sulfate. The organic layer was washed
 20 with saturated sodium bicarbonate and then brine, dried
 over sodium sulfate, filtered and concentrated to yield
 780 mg of crude material. Purification by silica gel
 chromatography using an eluant of 10:10:1 ethyl acetate:
 hexane:methanol provided 520 mg of Carbamic acid, [2R-
 25 hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl)
 amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-
 yl-ester, as a crystalline white solid. m.p.= 162-3°C,
 m/z= 553 (M+H).

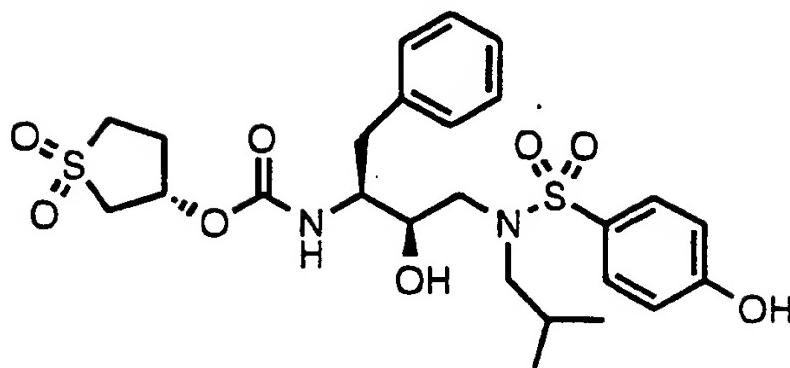
Example 16D

- 5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl ester
- 10 To a solution of 270 mg (0.5 mmol) of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester in 30 mL of dichloromethane was added 400 mg (1.2 mmol) of m-chloroperbenzoic acid (50 wt%) and the mixture was stirred for 12 hours. The contents were diluted with 10 mL of 10% aqueous sodium metabisulfite and stirred for 30 minutes. The organic layer was washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to yield 290 mg of crude product.
- 15 Purification by silica gel chromatography using an eluant of 10:10:1 ethyl acetate:hexane:methanol provided 260 mg of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl ester, as a white
- 20 crystalline solid. m.p.= 69 ° C, m/z = 569 (M+H).
- 25

Example 16E

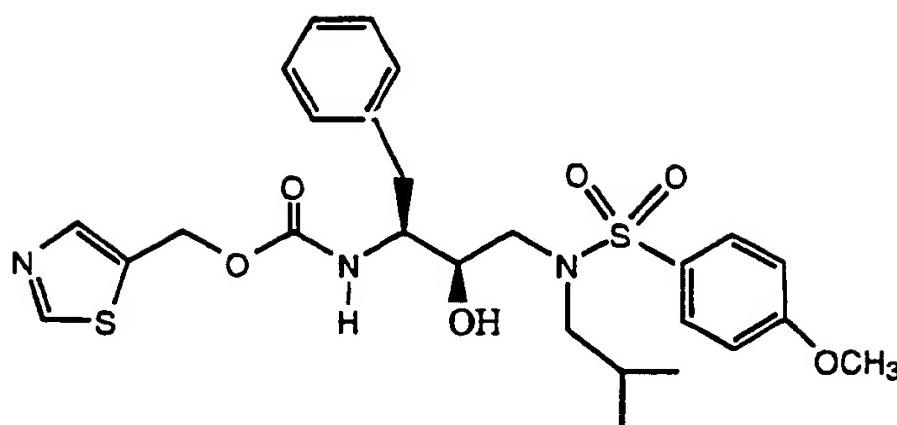
5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester.

To a solution of 125 mg (1.2 mmol) of 3-S-
 10 hydroxythiophene, 250 μ L of anhydrous pyridine, and 1 mL
 of dry acetonitrile was added 307 mg (1.2 mmol) of N,N'-
 dimethylsuccinimidyl carbonate and this suspension was
 stirred for 45 minutes. To this clear solution was added
 a solution of 445 mg (1.0 mmol) [2R-hydroxy-3-[(4-
 15 hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-
 (phenylmethyl)propylamine in 1.0 mL of acetonitrile and
 stirred for 12 hours. The contents were concentrated,
 and the residue was partitioned between ethyl acetate and
 5% aqueous potassium hydrogen sulfate. The organic layer
 20 was washed with saturated sodium bicarbonate and then
 brine, dried over sodium sulfate, filtered and
 concentrated to yield 460 mg of crude material.
 Purification by silica gel chromatography using an eluant
 of 10:10:1 ethyl acetate: hexane:methanol provided 235 mg
 25 of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl
 sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
 tetrahydrothiophen-3S-yl ester, as a crystalline white
 solid. m.p.= 184-85°C , m/z = 529 (M+Li).

Example 16F

- 5 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl ester]
- 10 To a solution of 125 mg (0.24 mmol) of carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, tetrahydrothiophen-3S-yl ester in 30 mL of dichloromethane was added 240 mg (0.7 mmol) of m-chloroperbenzoic acid (50 wt%) and the mixture
- 15 was stirred for 12 hours. The contents were diluted with 5 mL of 10% aqueous sodium metabisulfite and stirred for 30 minutes. The organic layer was washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to yield 110 mg of crude product.
- 20 Purification by silica gel chromatography using an eluant of 1:1 to 2:1 ethyl acetate:hexane:methanol provided 100 mg of carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 1,1-dioxotetrahydrothiophen-3S-yl-ester, as a white
- 25 crystalline solid, m.p.= 190°C, m/z= 561 (M+Li).

130

Example 17A

- 5 Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-
methoxyphenyl)sulfonyl](methylpropyl)aminol-1S-
(phenylmethyl)propyl]-, 5-thiazolylmethyl ester

Part A: Preparation of Methyl 2-aminothiazole-5-
 10 carboxylate

Methyl chloroacetate 190 g (1.75 mol) and methyl formate 111 g (1.80 mol), were added dropwise to a suspension of 100 g (1.8 mol) of sodium methoxide in 450 mL of dry 15 toluene at 5°C over 2 hours. After an additional 2.5 hours at 0°C. The contents were diluted with 600 mL of water and the layers separated. The aqueous phase was acidified with 113 mL of concentrated hydrochloric acid. The aqueous solution was placed in a 2 liter flask and 20 175 grams of thiourea was added and to solution was heated to reflux for 1.45 hours. To the cooled solution was added 25 g of DARCO activated charcoal and filtered through filter paper. The crude dark yellow solution was neutralized with 2.5 N sodium hydroxide upon which time 25 an amber solid precipitated which was filtered and air dried to yield 147 g of desired methyl 2-aminothiazole-5-carboxylate. m/e = 159 (M+H).

Part B: Preparation of Methyl 5-thiazolecarboxylate

To a solution of 35 mL (30.5 g, 260 mmol) of isoamyl nitrite in 120 mL of dioxane at 80°C under nitrogen, was
5 slowly added a slurry of 20.0 g (126 mmol) of methyl 2-amino-5-thiazolecarboxylate over a 45 minute period.
After refluxing for a further 1 hour, the solution was cooled, concentrated, dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over
10 magnesium sulfate, filtered and concentrated to afford 28 g of the crude product. This was chromatographed on 400 g of silica gel using 20% ethyl acetate/hexane to afford 9.07 g of purified material, which was crystallized from methylene chloride/hexane to yield 7.64g of pure methyl
15 5-thiazolylcarboxylate, m/e=144(M+H).

Part C: Preparation of 5-thiazolemethanol

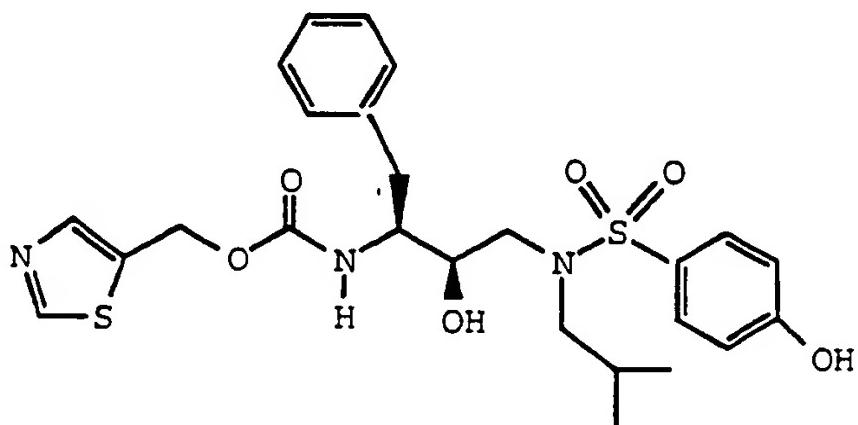
To a solution of 11.73 g (82 mmol) of methyl 5-thiazolylcarboxylate in 105 mL of anhydrous tetrahydrofuran at 0°C under nitrogen, was added 90 mL (90 mmol) of a 1.0M lithium aluminum hydride solution in diethyl ether over a 35 minute period. After stirring at room temperature for 30 minutes, the solution was cooled
25 to 0°C, and carefully quenched by the addition of 3 mL of water, 3 mL of 20% sodium hydroxide solution, and 6 mL of water, then 100mL of tetrahydrofuran was added. After stirring for 1 hour, the mixture was filtered, the solid was washed with tetrahydrofuran, and the filtrate
30 concentrated to afford 7.56 g of 5-thiazolylmethanol.

Part D: Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-(thiazolyl)methyl ester

35 To a solution of 115 mg (1.00 mmol) of 5-(hydroxymethyl) thiazole in 3 mL of anhydrous acetonitrile, was added 0.25 mL (0.25 g, 3.09 mmol) of pyridine and then 256 mg (1.03

mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 406 mg (1.00 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at 5 room temperature for 15 hours, ethyl acetate was added, washed with water, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 500mg of crude product. This was chromatographed on silica gel using 80% ethyl acetate/hexane as eluent to 10 afford 307 mg of a white solid, which was identified as the desired carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester, m/e = 548(M+H).

15

Example 17B

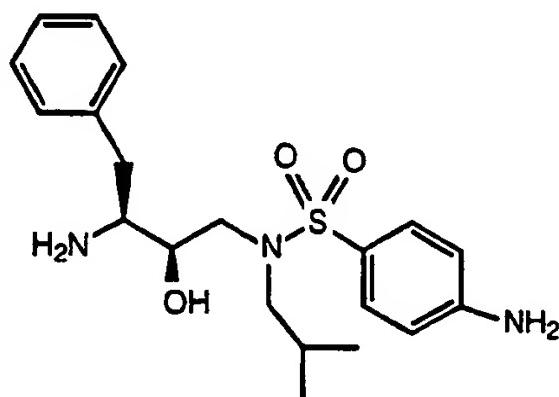
20 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 115 mg (1.00 mmol) of 5-(hydroxymethyl)thiazole in 3 mL of anhydrous acetonitrile, was added 0.25 mL (0.25 g, 3.09 mmol) of pyridine and then 256 mg (1.03 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 392 mg (1.00 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at 25 room temperature for 15 hours, ethyl acetate was added, washed with water, saturated sodium bicarbonate and brine,

dried over magnesium sulfate, filtered and concentrated to afford 450 mg of crude product. This was chromatographed on silica gel using 80% ethyl acetate/hexane as eluent to afford 270 mg of a white solid, which was identified as the 5 desired carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester, m/e =534 (M+H).

Example 18A

10



Preparation of 2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propylamine

15

Part A: Preparation of Carbamic acid, 2R-hydroxy-3-[(4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

20 To a solution of 4.0 g (10.8 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 50mL of anhydrous methylene chloride, was added 4.5mL (3.27g, 32.4 mmol) of triethylamine. The solution was cooled to 0°C and 2.63g (11.9 mmol) of 4-nitrobenzene
25 sulfonyl chloride was added, stirred for 30 minutes at 0°C, then for 1 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 5.9 g of crude material. This was recrystallized from ethyl acetate/hexane to afford 4.7 g of pure carbamic acid, [2R-hydroxy-3-[(4-nitrophenyl)sulfonyl](2-methylpropyl)

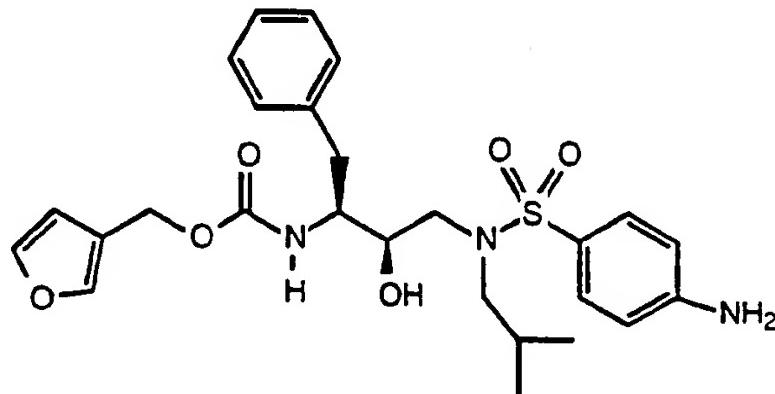
amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester;
m/e=556 (M+H).

Part B: Preparation of 2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

A solution of 3.0g (5.4 mmol) of carbamic acid, 2R-hydroxy-3-[(4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 20 mL of ethyl acetate was hydrogenated over 1.5 g of 10% palladium-on-carbon catalyst under 35 psig of hydrogen for 3.5 hours. The catalyst was removed by filtration and the solution concentrated to afford 2.05 g of the desired 2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine, m/e=392 (M+H).

Example 18B

20



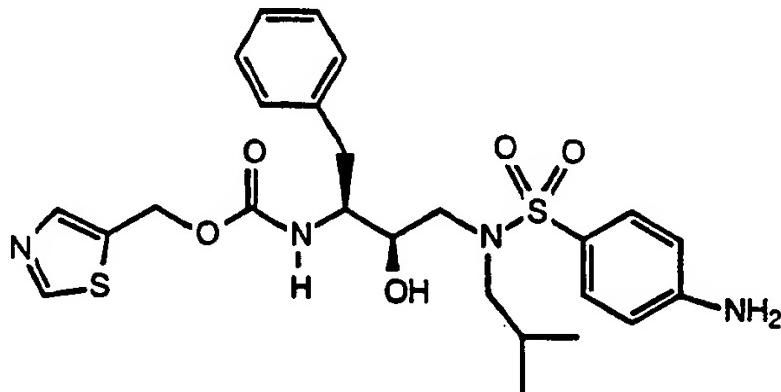
Preparation of Carbamic acid, 2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl-, 3-furanyl methyl ester

To a solution of 104mg (1.06 mmol) of 3-(hydroxymethyl)furan in 2 mL of anhydrous acetonitrile, was added 0.26 mL (0.25g, 3.18 mmol) of pyridine and then 277 mg (1.06 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 415 mg (1.06 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-

aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 72 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 550 mg of crude product. This was chromatographed on silica gel using 50% ethyl acetate/hexane as eluent to afford 230 mg of a white foam, which was identified as the desired carbamic acid, 2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-furanylmethyl ester, m/e = 522 (M+Li).

Example 18C

15



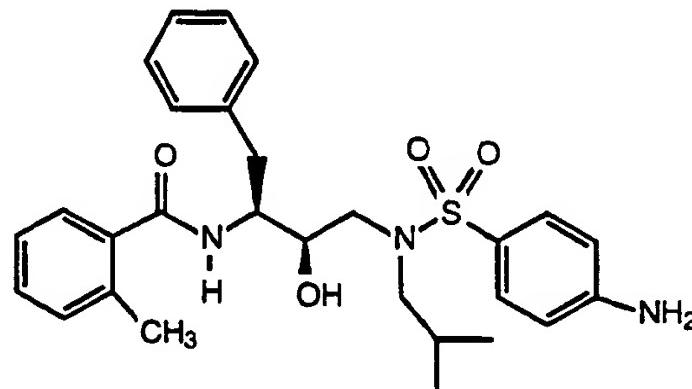
Preparation of Carbamic acid, 2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 118mg (1.03 mmol) of 5-(hydroxymethyl)thiazole in 3 mL of anhydrous acetonitrile, was added 0.25 mL (0.24g, 3.09 mmol) of pyridine and then 264 mg (1.03 mmol) of N,N'-disuccinimidyl carbonate at room temperature under nitrogen. After 45 minutes, 403 mg (1.03 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After stirring at room temperature for 15 hours, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford

350 mg of crude product. This was chromatographed on silica gel using 80% ethyl acetate/hexane as eluent to afford 290 mg of a white solid, which was identified as the desired carbamic acid, 2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester, m/e = 539 (M+Li).

Example 18D

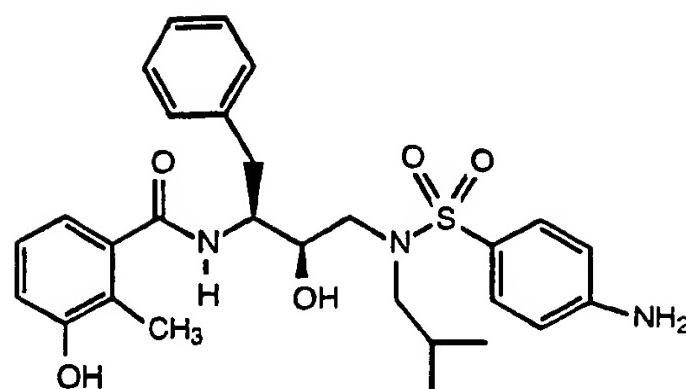
10



Preparation of Benzamide, N-[2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl

To a solution of 391 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 3 mL of anhydrous methylene chloride, was added 0.42 mL (3 mmol) of triethylamine, then at room temperature, 0.12 mL (0.9 mmol) of ortho-toluoyl chloride was added. After 15 hours at room temp ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 420 mg of crude material. This was chromatographed on 40 g of silica gel using 50% ethyl acetate/hexane to afford 368 mg of pure benzamide, N-[2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl, m/e=516 (M+Li).

30

Example 18E

5 Preparation of Benzamide, N-[2R-hydroxy-3-[1-(4-
aminophenyl)sulfonyl](2-methylpropyl)aminol-1S-
(phenylmethyl)propyl]-3-hydroxy-2-methyl

Part A: Preparation of 3-Hydroxy-2-methylbenzoic Acid

10

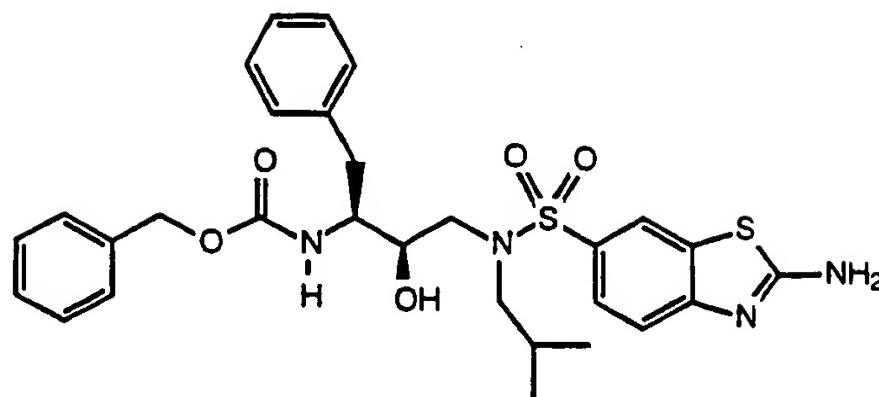
A one-necked 100 mL round-bottomed flask (magnetic stirring) was charged with 1.0 gram (6.6 mM) 3-amino-2-methylbenzoic acid. A warm mixture of 2.3 mL conc. sulfuric acid in 4.3 mL water was added to the flask, the resulting slurry was cooled below 15°C in an ice bath, and 6.6 grams of ice was added. The reaction mixture was treated via subsurface addition with a solution of 0.6 gram (8.6 mM) sodium nitrite in 6.6 mL ice water with the reaction temperature maintained at 0-5°C during the addition. After stirring at 0-5°C for 30 min., a few crystals of urea were added to decompose the excess nitrite. The reaction mixture was then poured into a room temperature solution of 23.8 grams (102.3 mM) copper (II) nitrate hemipentahydrate in 200 mL water. With vigorous stirring, the reaction mixture was treated with 0.9 gram (6.0 mM) copper (I) oxide. The reaction mixture foamed and changed from turquoise blue to dark green in color. Reaction was left stirring for 30 min. The reaction mixture was extracted with diethyl ether (3X), and the organic extracts were combined. The organic extracts were concentrated to approximately one-fourth the original volume, then extracted with 25 mL 1N sodium

hydroxide solution. The layers were separated, and the dark-red aqueous layer was acidified to pH=2 using 1N hydrochloric acid solution. The acidified aqueous layer was then extracted with diethyl ether (3X), and the ether extracts were combined, dried ($MgSO_4$), and concentrated to yield a reddish-colored oil. Purification by flash chromatography on silica gel using a gradient of 0-7% methanol/methylene chloride afforded 0.39 grams (36%) of a yellow solid.

10

Part B: Preparation of Benzamide, N-[2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

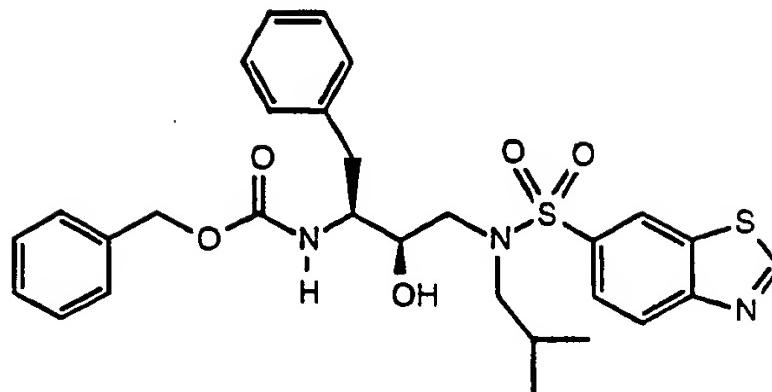
15 To a solution of 175 mg (1.15 mmol) of 3-hydroxy-2-methylbenzoic acid and 203 mg (1.5 mmol) of N-hydroxybenzotriazole in 6 mL of anhydrous N,N-dimethylformamide at 0°C, was added 220 mg (1.15 mmol) of EDC. After 20 minutes of activation at 0°C and 1 hour at 20 room temperature, 392 mg (1.0 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, 25 filtered and concentrated to afford 590 mg of crude material. This was chromatographed on silica gel using 50-80% ethyl acetate/methylene chloride as eluent to afford 255 mg of pure benzamide, N-[2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl, m/e = 526 (M+H). 30

Example 18E

5 Preparation of Carbamic acid, 2R-hydroxy-3-[(2-aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl- phenylmethyl ester

Carbamic acid, 2R-hydroxy-3-[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl- phenylmethyl ester 0.30 g (0.571 mmol) was added to a well mixed powder of anhydrous copper sulfate (1.20 g) and potassium thiocyanate (1.50 g) followed by dry methanol (6 mL) and the resulting black-brown suspension was heated at reflux for 2 hrs. The reaction mixture was filtered and the filtrate was diluted with water (5 mL) and heated at reflux. Ethanol was added to the reaction mixture, cooled and filtered. The filtrate upon concentration afforded a residue which was chromatographed (ethyl acetate:hexane 80:20) to afford 0.26 g (78%) of the desired compound as a solid.

140

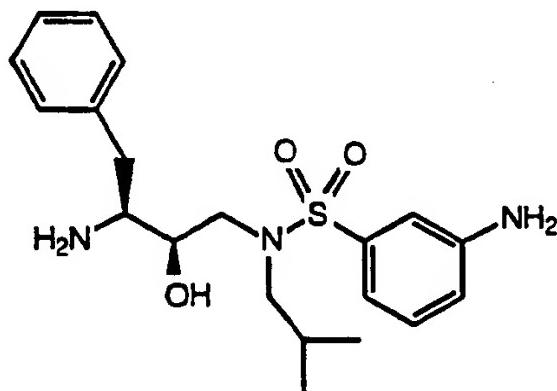
Example 18G

5 Preparation of Carbamic acid, 2R-hydroxy-3-[(benzothiazol-6-yl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl-, phenylmethyl ester

Carbamic acid, 2R-hydroxy-3-[(2-aminobenzothiazol-6-
10 yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
propyl-, phenylmethyl ester (0.25 g, 0.429 mmol) was
added to a solution of isoamyl nitrite (0.116 mL, 0.858
mmol) in dioxane (5 mL) and the mixture was heated at
85°C. After the cessation of evolution of nitrogen, the
15 reaction mixture was concentrated and the residue was
purified by chromatography (hexane:ethyl acetate 5:3) to
afford 0.130 g (53%) of the desired product as a solid.

Example 19A

20

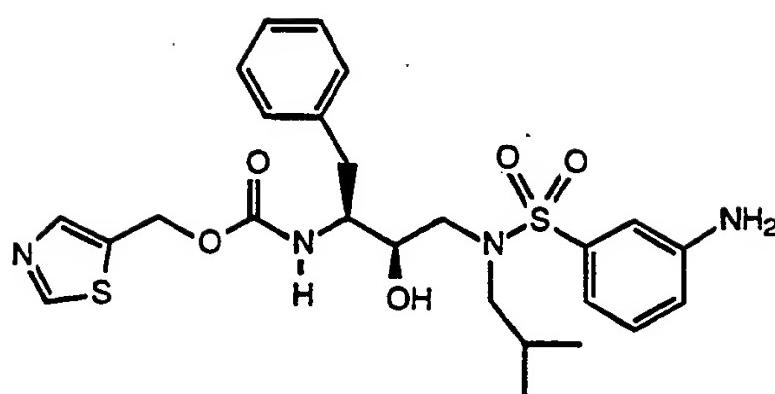


Preparation of 2R-hydroxy-3-[(3-aminophenyl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propylamine

25

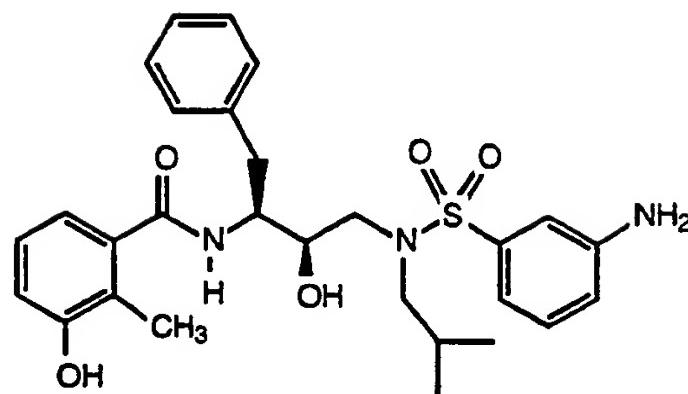
Part A: Preparation of Carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

- 5 To a solution of 1.1 g (3.0 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 15mL of anhydrous methylene chloride, was added 1.3mL (0.94g, 9.3 mmol) of triethylamine. The solution was cooled to 0°C and 0.67 g (3.0 mmol) of 3-nitrobenzene 10 sulfonyl chloride was added, stirred for 30 minutes at 0°C, then for 1 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 1.74 g of crude material. This was recrystallized from ethyl 15 acetate/hexane to afford 1.40 g of pure carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester, m/e=562 (M+Li).
- 20 Part B: Preparation of [2R-hydroxy-3-[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine
- A solution of 1.33g (2.5 mmol) of carbamic acid, [2R-25 hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 40 mL of 1:1 methanol/tetrahydrofuran was hydrogenated over 0.70 g of 10% palladium-on-carbon catalyst under 40 psig of hydrogen for 1.5 hours. The catalyst was removed by 30 filtration and the solution concentrated to afford 0.87 g of the desired [2R-hydroxy-3-[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine.

Example 19B

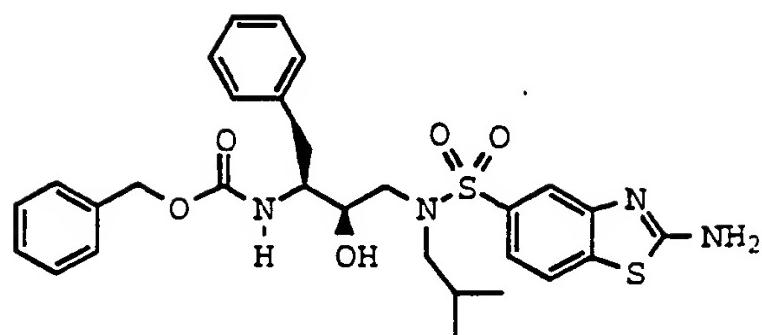
5 Preparation of Carbamic acid, 2R-hydroxy-3-[[(3-
aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 133mg (1.15 mmol) of 5-(hydroxymethyl)
10 thiazole in 3 mL of anhydrous acetonitrile, was added
0.30 mL (0.29g, 3.7 mmol) of pyridine and then 296 mg
(1.15 mmol) of N,N'-disuccinimidyl carbonate at room
temperature under nitrogen. After 60 minutes, 460 mg
(1.18 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(3-
15 aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine
was added. After stirring at room temperature for 15
hours, ethyl acetate was added, washed with 5% citric
acid, saturated sodium bicarbonate and brine, dried over
magnesium sulfate, filtered and concentrated to afford
20 480 mg of crude product. This was chromatographed on
silica gel using 50-80% ethyl acetate/hexane as eluent to
afford 422 mg of a white solid, which was identified as
the desired carbamic acid, 2R-hydroxy-3-[(3-aminophenyl
sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
25 5-thiazolylmethyl ester, m/e = 539 (M+Li).

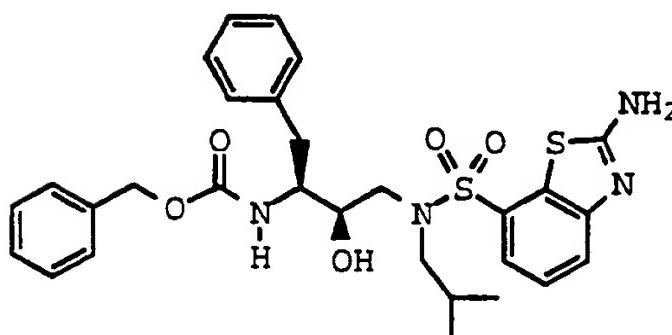
Example 19C

5 Preparation of Benzamide, N-[2R-hydroxy-3-[(3-
 aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-
 (phenylmethyl)propyl]-3-hydroxy-2-methyl

To a solution of 134 mg (0.88 mmol) of 3-hydroxy-2-methylbenzoic acid and 155 mg (1.15 mmol) of N-hydroxybenzotriazole in 5 mL of anhydrous N,N-dimethylformamide at 0°C, was added 167 mg (0.88 mmol) of EDC. After 20 minutes of activation at 0°C and 1 hour at room temperature, 300 mg (1.0 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(3-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 330 mg of crude material. This was chromatographed on silica gel using 30-70% ethyl acetate/methylene chloride as eluent to afford 230 mg of pure benzamide, N-[2R-hydroxy-3-[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl.

Example 19D

and



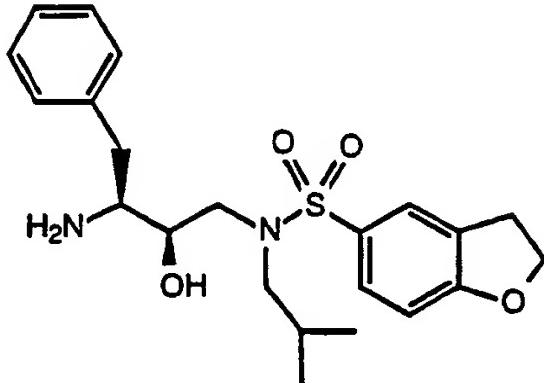
- 5 Preparation of Carbamic acid, 2R-hydroxy-3-[(2-amino
benzothiazol-5-yl)sulfonyl](2-methylpropyl)aminol-1S-
(phenylmethyl)propyl-, phenylmethyl ester; and Carbamic
acid, 2R-hydroxy-3-[(2-aminobenzothiazol-7-yl)sulfonyl]
(2-methylpropyl)aminol-1S-(phenylmethyl)propyl-
10 phenylmethyl ester

The carbamic acid, 2R-hydroxy-3-[(3-aminophenylsulfonyl)
(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
phenylmethyl ester 0.36 g (0.685 mmol) was added to a
15 well mixed powder of anhydrous copper sulfate (1.44 g)
and potassium thiocyanate (1.80 g) followed by dry
methanol (10 mL) and the resulting black-brown suspension
was heated at reflux for 2 hrs. The reaction mixture was
filtered and the filtrate was diluted with water (5 mL)
20 and heated at reflux. Ethanol was added to the reaction
mixture, cooled and filtered. The filtrate upon
concentration afforded a residue which was
chromatographed (ethyl acetate:hexane 1:1) to afford 0.18
g (45%) of the 7-isomer as a solid. Further elution of

the column with (ethyl acetate:hexane 3:2) afforded 0.80 g (20%) afforded the 5-isomer as a solid.

Example 20A

5



Preparation of 2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-

y1)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)

10 propylamine

Part A: Preparation of 5-(2,3-dihydrobenzofuranyl)sulfonyl chloride

15 To a solution of 3.35g of anhydrous N,N-dimethylformamide at 0°C under nitrogen was added 6.18 g of sulfonyl chloride, whereupon a solid formed. After stirring for 15 minutes, 4.69 g of 2,3-dihydrobenzofuran was added, and the mixture heated at 100°C for 2 hours. The
20 reaction was cooled, poured into ice water, extracted with methylene chloride, dried over magnesium sulfate, filtered and concentrated the crude material. This was recrystallized from ethyl acetate to afford 2.45 g of 5-(2,3-dihydrobenzofuranyl)sulfonyl chloride.

25

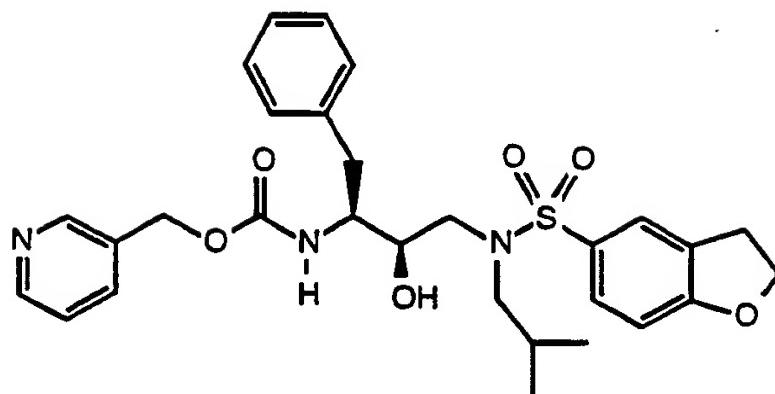
Part B: Preparation of Carbamic acid, 2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

30 To a solution of 1.11 g (3.0 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 20mL of anhydrous methylene chloride, was added 1.3mL

(0.94 g, 9.3 mmol) of triethylamine. The solution was cooled to 0°C and 0.66 g of 5-(2,3-dihydrobenzofuranyl)sulfonyl chloride was added, stirred for 15 minutes at 0°C, then for 2 hour at room temperature. Ethyl acetate
5 was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 1.62 g of crude material. This was recrystallized from diethyl ether to afford 1.17 g of pure carbamic acid,
[2R-hydroxy-3-[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
10 methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester.

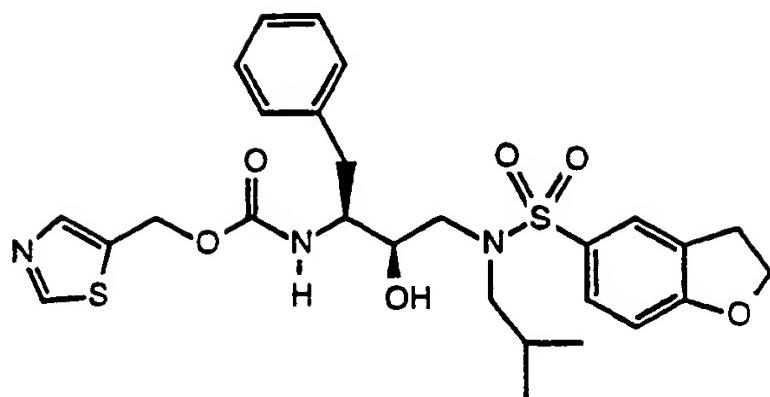
Part C: Preparation of [2R-hydroxy-3-[(2,3-dihydro
benzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
15 (phenylmethyl)propylamine

A solution of 2.86 g of carbamic acid, [2R-hydroxy-3-
[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)
amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 30
20 mL of tetrahydrofuran was hydrogenated 0.99g of 10% palladium-on-carbon under 50 psig of hydrogen for 16 hours. The catalyst was removed by filtration and the filtrate concentrated to afford 1.99 g of the desired [2R-hydroxy-3-[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
25 methylpropyl)amino]-1S-(phenylmethyl)propylamine.

Example 20B

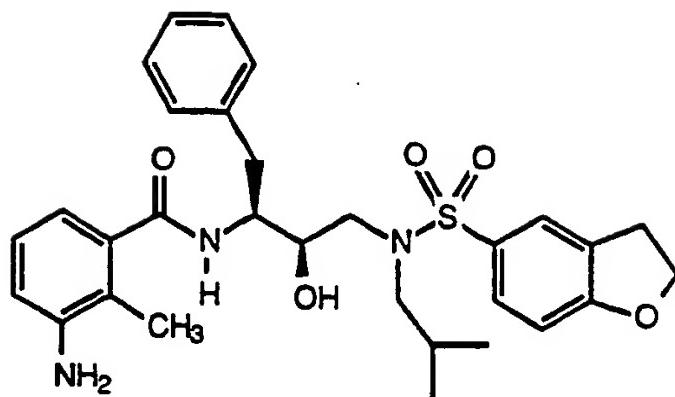
5 Preparation of Carbamic acid, [2R-hydroxy-3-[(2,3-
dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-
1S-(phenylmethyl)propyl-, 3-pyridylmethyl ester

To a solution of 110 mg of 3-pyridylcarbinol in 3 mL of
10 anhydrous acetonitrile, was added 0.24g of anhydrous
pyridine and then 260 mg of N,N'-disuccinimidyl carbonate
at room temperature under nitrogen. After 45 minutes,
420 mg of 2R-hydroxy-3-[(2-methylpropyl)(2,3-
dihydrobenzofuran-5-yl)sulfonyl]amino-1S-(phenylmethyl)
15 propylamine was added. After stirring at room
temperature for 20 hours, ethyl acetate was added, washed
with 5% citric acid, saturated sodium bicarbonate and
brine, dried over magnesium sulfate, filtered and
concentrated to afford 320 mg of crude product. This was
20 chromatographed on silica gel using 50% ethyl
acetate/hexane as eluent to afford 260 mg of a white
solid, which was identified as the desired carbamic acid,
[2R-hydroxy-3-[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-
25 pyridylmethyl ester.

Example 20C

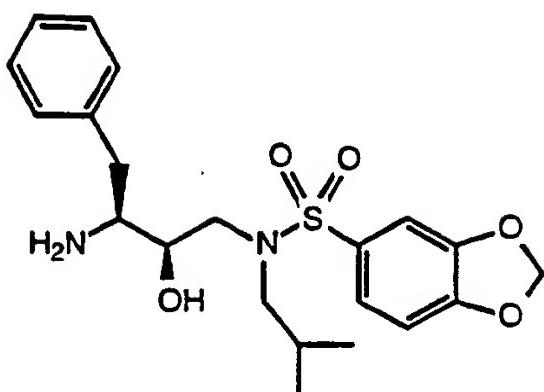
5 Preparation of Carbamic acid, [2R-hydroxy-3-[(2,3-
dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino-
1S-(phenylmethyl)propyl-, 5-thiazolylmethyl ester

To a solution of 66 mg of 5-(hydroxymethyl)thiazole in 3
10 mL of anhydrous acetonitrile, was added 0.14g of
anhydrous pyridine and then 150 mg of N,N'-disuccinimidyl
carbonate at room temperature under nitrogen. After 45
minutes, 240 mg of 2R-hydroxy-3-[(2-methylpropyl)(2,3-
dihydrobenzofuran-5-yl)sulfonyl]amino-1S-(phenylmethyl)
15 propylamine was added. After stirring at room
temperature for 20 hours, ethyl acetate was added, washed
with 5% citric acid, saturated sodium bicarbonate and
brine, dried over magnesium sulfate, filtered and
concentrated to afford 220 mg of crude product. This was
20 chromatographed on silica gel using 50% ethyl
acetate/hexane as eluent to afford 120 mg of a white
solid, which was identified as the desired carbamic acid,
[2R-hydroxy-3-[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-
25 thiazolylmethyl ester.

Example 20D

5 Preparation of Benzamide, N-[2R-hydroxy-3-[(2,3-
dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-
1S-(phenylmethyl)propyl-3-amino-2-methyl-

To a solution of 175 mg of 3-amino-2-methylbenzoic acid
10 in 2 mL of anhydrous N,N-dimethylformamide at 0°C, was
added 200 mg of N-hydroxybenzotriazole and then 210 mg of
EDC. After 20 minutes of activation, 405 mg of 2R-
hydroxy-3-[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propylamine was
15 added. After stirring at room temperature for 16 hours,
ethyl acetate was added, washed with 5% citric acid,
sodium bicarbonate, brine, dried over magnesium sulfate,
filtered and concentrated to afford 225 mg of crude
product. This was chromatographed on silica gel using
20 50% ethyl acetate/hexane to afford 140 mg of the desired
benzamide, N-[2R-hydroxy-3-[(2,3-dihydrobenzofuran-5-
yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)
propyl-3-amino-2-methyl, m/e=552 (M+H).

Example 21A

5 Preparation of 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

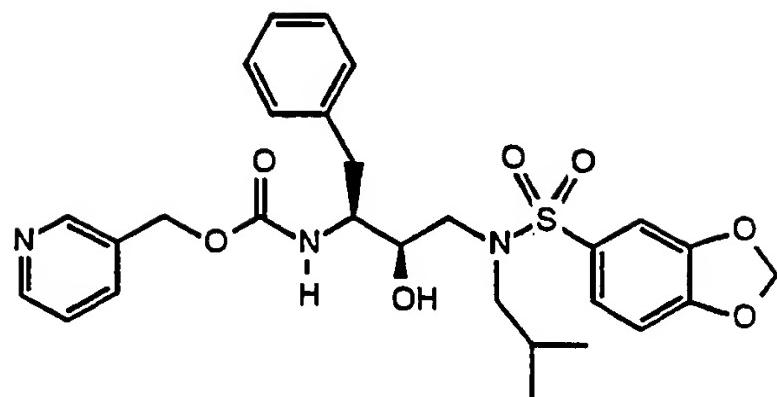
10 Part A: Preparation of (1,3-Benzodioxol-5-yl)sulfonyl chloride

To a solution of 4.25 g of anhydrous N,N-dimethylformamide at 0°C under nitrogen was added 7.84g of sulfonyl chloride, whereupon a solid formed. After stirring for 15 minutes, 6.45 g of 1,3-benzodioxole was added, and the mixture heated at 100°C for 2 hours. The reaction was cooled, poured into ice water, extracted with methylene chloride, dried over magnesium sulfate, filtered and concentrated to give 7.32 g of crude material as a black oil. This was chromatographed on silica gel using 20% methylene chloride/hexane to afford 1.9 g of (1,3-benzodioxol-5-yl)sulfonyl chloride.

25 Part B: Preparation of Carbamic acid, 2R-hydroxy-3-[[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

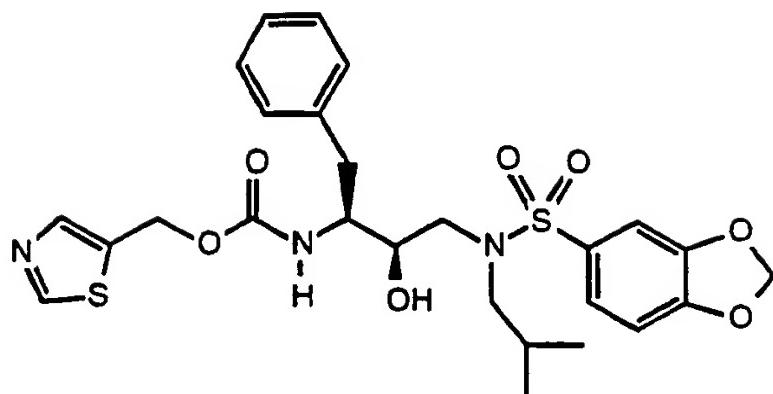
To a solution of 3.19 g(8.6 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 30 40mL of anhydrous methylene chloride, was added 0.87g of triethylamine. The solution was cooled to 0°C and 1.90g of (1,3-benzodioxol-5-yl)sulfonyl chloride was added,

- stirred for 15 minutes at 0°C, then for 17 hours at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield crude material. This was
5 recrystallized from diethyl ether/hexane to afford 4.77 g of pure carbamic acid, 2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester.
- 10 Part C: Preparation of 2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine
- A solution of 4.11 g of carbamic acid, 2R-hydroxy-3-
15 [(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 45 mL of tetrahydrofuran and 25 mL of methanol was hydrogenated over 1.1 g of 10% palladium-on-carbon under 50 psig of hydrogen for 16 hours. The catalyst was removed by
20 filtration and the filtrate concentrated to afford 1.82g of the desired 2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine.

Example 21B

5 Preparation of Carbamic acid, 2R-hydroxy-3-[(1,3-
benzodioxol-5-yl)sulfonyl](2-methylpropyl)aminol-1S-
(phenylmethyl)propyl-, 3-pyridylmethyl ester

To a solution of 110 mg of 3-pyridylcarbinol in 3 mL of
10 anhydrous acetonitrile, was added 0.24 g of anhydrous
pyridine and then 260 mg of N,N'-disuccinimidyl carbonate
at room temperature under nitrogen. After 45 minutes,
410 mg of 2R-hydroxy-3-[(1,3-benzodioxol-5-
y1)sulfonyl](2-methylpropyl)amino]-1S-
15 (phenylmethyl)propylamine was added. After stirring at
room temperature for 20 hours, ethyl acetate was added,
washed with 5% citric acid, saturated sodium bicarbonate
and brine, dried over magnesium sulfate, filtered and
concentrated to afford 330 mg of crude product. This was
20 chromatographed on silica gel using 50% ethyl
acetate/hexane as eluent to afford 160 mg of a white
solid, which was identified as the desired carbamic acid,
[2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-
25 pyridylmethyl ester, m/e=562(M+Li).

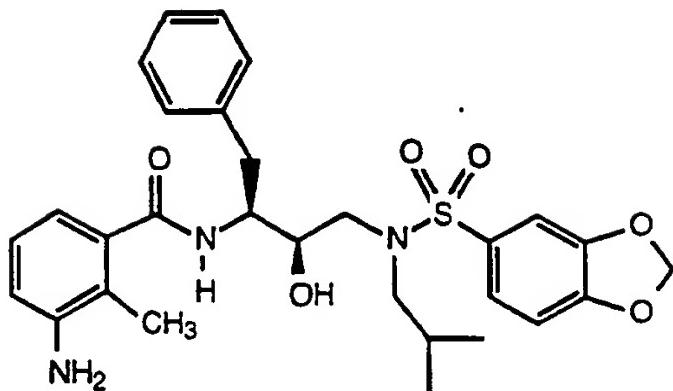
Example 21C

5 Preparation of Carbamic acid, 2R-hydroxy-3-[(1,3-
benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-

(phenylmethyl)propyl-, 5-thiazolylmethyl ester

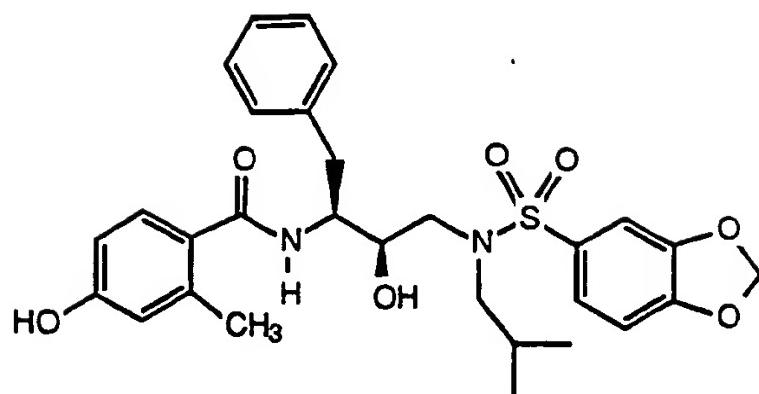
To a solution of 85 mg (0.8 mmol) of 5-(hydroxymethyl)
10 thiazole in 2.2 mL of anhydrous acetonitrile, was added
0.18 mL (2.2 mmol) of anhydrous pyridine and then 189 mg
(0.74 mmol) of N,N'-disuccinimidyl carbonate at room
temperature under nitrogen. After 45 minutes, 310 mg of
2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-
15 methylpropyl)amino]-1S-(phenylmethyl)propylamine was
added. After stirring at room temperature for 20 hours,
ethyl acetate was added, washed with 5% citric acid,
saturated sodium bicarbonate and brine, dried over
magnesium sulfate, filtered and concentrated to afford
20 300 mg of crude product. This was chromatographed on
silica gel using 50% ethyl acetate/hexane as eluent to
afford 150 mg of a white solid, which was identified as
the desired carbamic acid, 2R-hydroxy-3-[(1,3-
benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-

25 (phenylmethyl)propyl-, 5-thiazolylmethyl ester,
m/e=568 (M+Li).

Example 21D

5 Preparation of Benzamide, N-[2R-hydroxy-3-[(1,3-
benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-3-amino-2-methyl

To a solution of 175 mg of 3-amino-2-methylbenzoic acid
10 in 2 mL of anhydrous N,N-dimethylformamide at 0°C, was
added 200 mg of N-hydroxybenzotriazole and then 210 mg of
EDC. After 20 minutes of activation, 410 mg of 2R-
hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propylamine was
15 added. After stirring at room temperature for 16 hours,
ethyl acetate was added, washed with 5% citric acid,
sodium bicarbonate, brine, dried over magnesium sulfate,
filtered and concentrated to afford 500 mg of crude
product. This was chromatographed on silica gel using
20 50% ethyl acetate/hexane to afford 310 mg of the desired
benzamide, N-[2R-hydroxy-3-[(1,3-benzodioxol-5-
yl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-3-amino-2-methyl, m/e=560 (M+Li).

Example 21E

- 5 Preparation of Benzamide, N-[2R-hydroxy-3-[[(1,3-
benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-4-hydroxy-2-methyl

Part A: Preparation of 2-Trimethylsilyloxy-1,3-cyclohexadiene

A 100 mL round bottom flask equipped with magnetic stir bar, addition funnel, and N₂ inlet was charged with 40 mL dry THF and 8.3 mL diisopropyl amine. The solution was cooled to -78°C and charged with 23.8 mL of 2.5M nBuLi in Hexane. After 10 minutes a solution of 5.2 g cyclohexenone in 10 mL THF was added dropwise. The reaction was stirred 10 minutes at -78°C and quenched with 7.5 mL trimethylsilyl chloride. The reaction was stirred 15 minutes and then partitioned between diethyl ether and cold saturated aqueous sodium bicarbonate. The combined organic layers were dried over sodium sulfate and concentrated in vacuo to a yellow oil. Short path distillation (BP 27-29°C/0.5mm) afforded 6.0 g (66%) of 2-Trimethylsilyloxy-1,3-Cyclohexadiene.

Part B: Preparation of Methyl (2-methyl-4-trimethylsilyloxy)benzoate

A 50 mL round bottom flask equipped with magnetic stir bar and condenser was charged with 6.0 g of 2-trimethylsilyloxy-1,3-cyclohexadiene, 3.5 g methyl

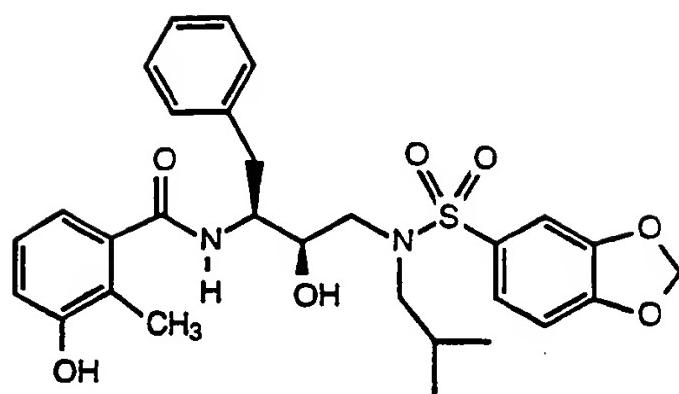
tetrolate in 3 mL dry toluene. The reaction was heated to 150°C for 50 hours at which point ¹H-NMR indicated no starting diene. The reaction was concentrated in vacuo to provide 5.7 g (67%) methyl 2-methyl-4-
5 trimethylsilyloxybenzoate.

Part C: Preparation of 4-Hydroxy-2-methylbenzoic acid

A 100mL round bottom flask equipped with magnetic stir
10 bar was charged with 5.7 g methyl 2-methyl-4-
trimethylsilyloxybenzoate and 2.0 g LiOH in 40 mL
methanol and 10 mL water. After 2 hours at reflux the
reaction was poured into 10 mL concentrated HCl and then
100 g ice. Extraction with ethyl acetate followed by
15 concentration in vacuo gave a crude solid (70:30)
product:starting material. Flash Chromatography using
50-50 ethyl acetate/hexanes as an eluent gave 1.15 g 2-
methyl-4-hydroxybenzoic acid, m/e=193 (M+H).

20 Part D: Preparation of Benzamide, N-[2R-hydroxy-3-
[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-
1S-(phenylmethyl)propyl]-4-hydroxy-2-methyl

To a solution of 175 mg of 4-hydroxy-2-methylbenzoic acid
25 in 2 mL of anhydrous N,N-dimethylformamide at 0°C, was
added 200 mg of N-hydroxybenzotriazole and then 220 mg of
EDC. After 20 minutes of activation, 450 mg of 2R-
hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propylamine was
30 added. After stirring at room temperature for 16 hours,
ethyl acetate was added, washed with 5% citric acid,
sodium bicarbonate, brine, dried over magnesium sulfate,
filtered and concentrated to afford crude product. This
was chromatographed on silica gel using 50% ethyl
35 acetate/hexane to afford 102 mg of the desired benzamide,
N-[2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-
methylpropyl)amino]-1S-(phenylmethyl)propyl]-4-hydroxy-2-
methyl.

Example 21F

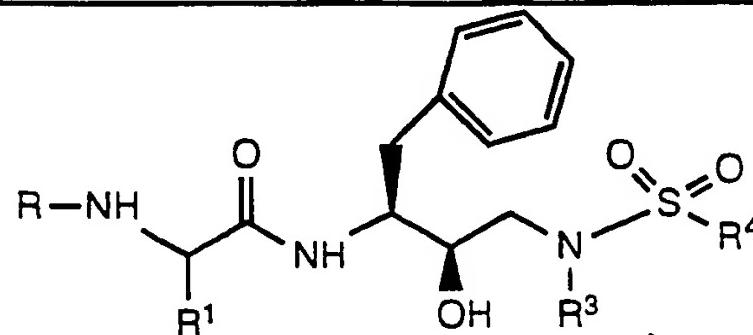
5

Preparation of Benzamide, N-[2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

- 10 To a solution of 187 mg (1.23 mmol) of 3-hydroxy-2-methylbenzoic acid and 217 mg (1.61 mmol) of N-hydroxybenzotriazole in 6 mL of anhydrous N,N-dimethylformamide at 0°C, was added 236 mg (1.23 mmol) of EDC. After 20 minutes of activation at 0°C and 1 hour at room temperature, 450 mg (1.07 mmol) of 2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 650 mg of crude material. This was chromatographed on silica gel using 0-25% ethyl acetate/methylene chloride as eluent to afford 390 mg of pure benzamide, N-[2R-hydroxy-3-[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl, m/e=561(M+Li).
- 15
- 20
- 25

Example 22

Following the procedures of Examples 1-21, the compounds shown in Tables 3, 5A and 5B were prepared and in Tables 5 4 through 17 can be prepared.

TABLE 3

10

Entry No.	R	R ¹	R ³	R ⁴	
1	Cbz	t-Butyl	i-Amyl	Methyl	
2	N,N-Dimethylglycine	t-Butyl	i-Amyl	Methyl	
3	Cbz	i-Propyl	i-Amyl	Phenyl	
15	4	Cbz	sec-Butyl	i-Amyl	Phenyl
5	Cbz	CH ₂ C(O)NH ₂	n-Propyl	Phenyl	
6	N-Methylglycine	t-Butyl	i-Amyl	Phenyl	
7	Cbz	t-Butyl	i-Butyl	Phenyl	
8	N,N-Dimethylglycine	t-Butyl	i-Amyl	Phenyl	
20	9	N-Methylglycine	t-Butyl	i-Amyl	Phenyl
10	N,N-Dimethylglycine	t-Butyl	i-Butyl	(4-OCH ₃)Phenyl	
11	N-Methylglycine	t-Butyl	i-Butyl	(4-OCH ₃)Phenyl	

TABLE 4

 5

Entry No.	R	R ³	R ⁴
10	1 Cbz ^a	CH ₃	n-Butyl
	2 Cbz	i-Butyl	CH ₃
	3 Cbz	i-Butyl	n-Butyl
	4 Q ^b	i-Butyl	n-Butyl
	5 Cbz	i-Propyl	n-Butyl
	15 6 Q	i-Propyl	n-Butyl
		C ₆ H ₅	n-Butyl
	7 Cbz	-CH ₂ -C ₆ H ₅	n-Butyl
	8 Cbz	-CH ₂ -C ₆ H ₄ -CH ₃	n-Butyl
	9 Cbz	-CH ₂ -C ₆ H ₄ -CH ₃	n-Butyl
	10 Q	-CH ₂ -C ₆ H ₄ -CH ₃	n-Butyl
	20 11 Cbz	-C ₆ H ₅	n-Butyl
	12 Cbz	i-Butyl	n-Propyl

TABLE 4 (Cont'd.)

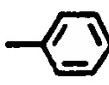
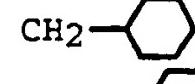
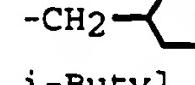
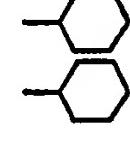
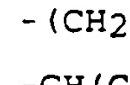
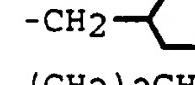
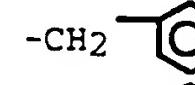
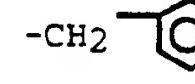
Entry No.	R	R ³	R ⁴	
5				
13	Cbz	i-Butyl	-CH ₂ CH(CH ₃) ₂	
14	Cbz	(R)-CH(CH ₃) 	n-Butyl	
15	Cbz	CH ₂ 	i-Propyl	
16	Cbz	-CH ₂ 	-CH ₂ CH ₂ CH(CH ₃) ₂	
10	17	Cbz	i-Butyl	-CH ₂ CH ₃
	18	Cbz	i-Butyl	-CH(CH ₃) ₂
	19	Cbz	i-Butyl	
	20	Q	-Butyl	
	21	Cbz	-CH ₂ 	- (CH ₂) ₂ CH(CH ₃) ₂
15	22	Cbz	(CH ₂) ₂ CH(CH ₃) ₂	-CH(CH ₃) ₂
	23	Q	i-Butyl	-CH(CH ₃) ₂
	24	Cbz	i-Butyl	-C(CH ₃) ₃
	25	Q	i-Butyl	-C(CH ₃) ₃
	26	Cbz	-CH ₂ 	-C(CH ₃) ₃
20	27	Q	-CH ₂ 	-C(CH ₃) ₃
	28	Cbz	- (CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃
	29	Q	- (CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃
	30	Cbz	-CH ₂ C ₆ H ₅	-C(CH ₃) ₃
	31	Q	-CH ₂ C ₆ H ₅	-C(CH ₃) ₃
25	32	Cbz	- (CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃
	33	Cbz	- (CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃
	34	Cbz	n-Butyl	-C(CH ₃) ₃

TABLE 4 (Cont'd.)

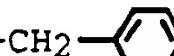
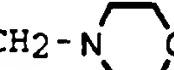
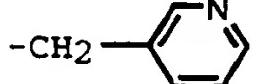
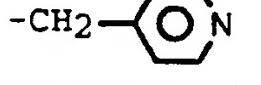
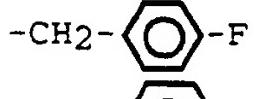
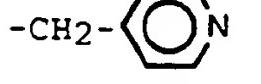
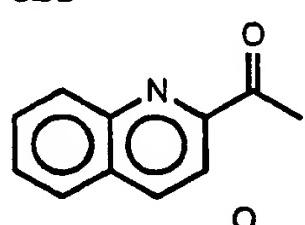
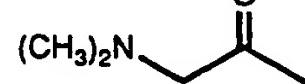
Entry No.	R	R ³	R ⁴
5			
35	Cbz	n-Pentyl	-C(CH ₃) ₃
36	Cbz	n-Hexyl	-C(CH ₃) ₃
37	Cbz	-CH ₂ - 	-C(CH ₃) ₃
38	Cbz	-CH ₂ C(CH ₃) ₃	-C(CH ₃) ₃
10	39	Q	-CH ₂ C(CH ₃) ₃
	40	Cbz	-CH ₂ CH ₂ -N 
	41	Cbz	-CH ₂ C ₆ H ₅ OCH ₃ (para)
	42	Cbz	-CH ₂ - 
	43	Cbz	-CH ₂ - 
15	44	Cbz	- (CH ₂) ₂ C(CH ₃) ₃
	45	Q	- (CH ₂) ₂ C(CH ₃) ₃
	46	Cbz	- (CH ₂) ₄ OH
	47	Q	- (CH ₂) ₄ OH
	48	Q	-CH ₂ - 
20	49	Q	-CH ₂ - 
	50	Cbz	-CH ₂ CH(CH ₃) ₂
	51		-CH ₂ CH(CH ₃) ₂
	52		-CH ₂ CH(CH ₃) ₂

TABLE 4 (Cont'd.)

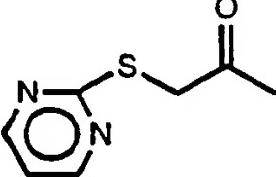
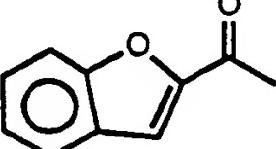
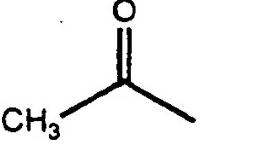
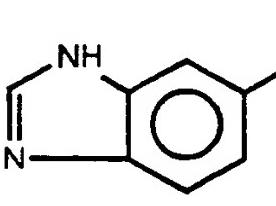
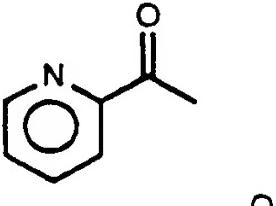
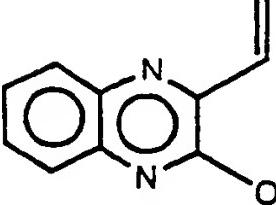
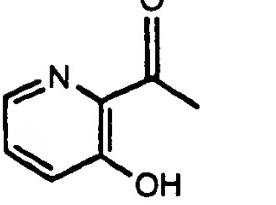
Entry No.	R	R ³	R ⁴	
5				
53		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	
54		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	
55		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	
56		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	
10	57		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
	58		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
	59		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅

TABLE 4 (Cont'd.)

Entry No.	R	R ³	R ⁴
5			
60		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
61		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
62		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
63		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
10	64		-CH ₂ CH(CH ₃) ₂
	65		-CH ₂ CH(CH ₃) ₂

TABLE 4 (Cont'd.)

Entry No.	R	R ³	R ⁴
5			
66		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
67		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
68		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
69		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
10	70 Q	-CH ₂ Ph	-Ph
	71 Q	-CH ₂ --F	-Ph
	72 Q	-CH ₂ -	-Ph
	73 Q	-CH ₂ -	-Ph
	74 Q	-CH ₂ -	-Ph

TABLE 4 (Cont'd.)

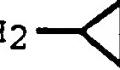
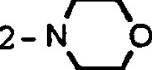
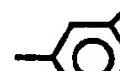
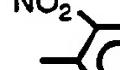
Entry No.	R	R ³	R ⁴
5			
75	Q	-CH ₂ 	-Ph
76	Q	-CH ₂ CH=CH ₂	-Ph
77	Q	- 	-Ph
78	Q	- 	-Ph
10	79	Q	-CH ₂ CH ₂ Ph
	80	Q	-CH ₂ CH ₂ CH ₂ CH ₂ OH
	81	Q	-CH ₂ CH ₂ N(CH ₃) ₂
	82	Q	-CH ₂ CH ₂ - 
	83	Q	-CH ₃
15	84	Q	-CH ₂ CH ₂ CH ₂ SCH ₃
	85	Q	-CH ₂ CH ₂ CH ₂ S(O)OCH ₃
	86	Q	-CH ₂ CH ₂ CH ₂ CH(CH ₃) ₂
	87	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
	88	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
20	89	Q	-CH ₂ CH ₂ CH ₂ CH(CH ₃) ₂
	90	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
	91	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
	92	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
	93	Q	-CH ₂ CH ₂ CH(CH ₃) ₂

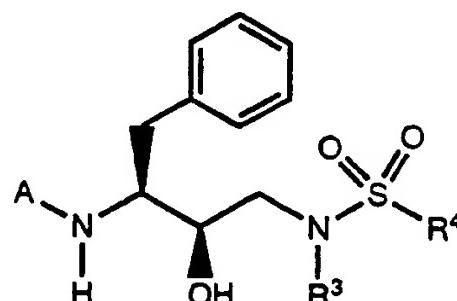
TABLE 4 (Cont'd.)

Entry No.	R	R ³	R ⁴
5			
94	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -OCH ₃
95	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-  NO ₂
96	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-  NO ₂
97	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-  CF ₃
10	98	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
	99	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
	100	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
	101	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
	102	Q	-CH ₂ CH ₂ CH(CH ₃) ₂
15	103	Q	-CH ₂ CH(CH ₃) ₂
	104	Q	-CH ₂ CH(CH ₃) ₂
	105	Q	-CH ₂ CH(CH ₃) ₂
	106	Q	-CH ₂ CH ₂ CH ₃
	107	Q	-CH ₂ CH ₂ CH ₂ CH ₃

20 a benzylloxycarbonyl

b 2-quinolinylcarbonyl

TABLE 5



5

	Entry	A	R ³	R ⁴
10	1	Cbz-Val	i-amyl	-C ₆ H ₅
	2	Cbz-Leu	i-amyl	-C ₆ H ₅
	3	Cbz-Ile	i-amyl	-C ₆ H ₅
	4	Ac-D-homo-Phe	i-Bu	methyl
	5	Qui-Orn(g-Cbz)	-CH ₂ -	-C ₆ H ₅
15	6	Cbz-Asn	-CH ₂ CH=CH ₂	-C ₆ H ₅
	7	Acetyl-t-BuGly	i-amyl	-C ₆ H ₅
	8	Acetyl-Phe	i-amyl	-C ₆ H ₅
	9	Acetyl-Ile	i-amyl	-C ₆ H ₅
	10	Acetyl-Leu	i-amyl	-C ₆ H ₅
20	11	Acetyl-His	i-amyl	-C ₆ H ₅
	12	Acetyl-Thr	i-amyl	-C ₆ H ₅
	13	Acetyl-NHCH(C(CH ₃) ₂ (SCH ₃))C(O)-	i-amyl	-C ₆ H ₅
	14	Cbz-Asn	i-amyl	-C ₆ H ₅
	15	Cbz-Ala	i-amyl	-C ₆ H ₅
25	16	(N,N-dimethylglycinyl)Val	i-amyl	-C ₆ H ₅
	17	(N-methylglycinyl)Val	i-amyl	-C ₆ H ₅
	18	(N,N-dimethylglycinyl)Ile	i-amyl	-C ₆ H ₅
	19	(N-methylglycinyl)Ile	i-amyl	-C ₆ H ₅

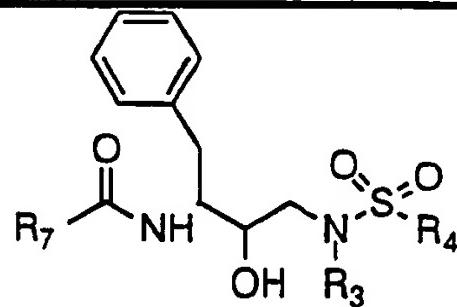
TABLE 5 (Cont'd)

Entry	A	R ³	R ⁴
5			
20	Cbz-Ala	i-amyl	-C ₆ H ₅
21	Cbz-beta-cyanoAla	i-amyl	-C ₆ H ₅
22	Cbz-t-BuGly	i-amyl	-C ₆ H ₅
23	Q-t-BuGly	i-amyl	-C ₆ H ₅
10	24 Q-SCH ₃ Cys	i-amyl	-C ₆ H ₅
	25 Cbz-SCH ₃ Cys	i-amyl	-C ₆ H ₅
	26 Q-Asp	i-amyl	-C ₆ H ₅
	27 Cbz-(NHCH(C(CH ₃) ₂ (SCH ₃))C(O)-	i-amyl	-C ₆ H ₅
	28 Cbz-EtGly	i-amyl	-C ₆ H ₅
15	29 Cbz-PrGly	i-amyl	-C ₆ H ₅
	30 Cbz-Thr	i-amyl	-C ₆ H ₅
	31 Q-Phe	i-amyl	-C ₆ H ₅
	32 Cbz-Phe	i-amyl	-C ₆ H ₅
	33 CH ₂ =CHCH ₂ -O-C=O	i-Butyl	-C ₆ H ₄

TABLE 5A

Entry

5



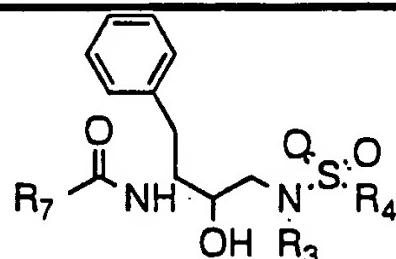
MASS MEASUREMENT

	R^3	R^4	R^7	MOL FORM	CALC $\text{M}+\text{H}$	FOUND
1				$\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$	503.2661	503.2624
2				$\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_5\text{S}$	517.2736	517.2777
3				$\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_5\text{S}$	531.2893	531.2916
4				$\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_5\text{S}$	565.2736	565.2731
5				$\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_5\text{S}$	550.2376	550.2427

TABLE 5A (Cont'd)

Entry

5

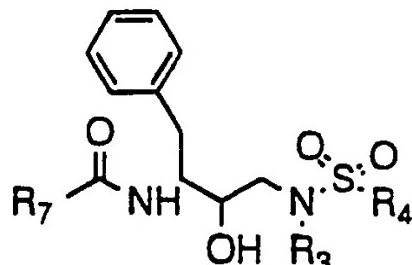


	MASS MEASUREMENT					
	R^3	R^4	R^7	MOL FORM	CALC	FOUND
6	CH_2CH_3	OCH_3	CH_3	$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$	539($\text{M}+\text{H}$)	539
7			CH_3	$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$?	?
8			CH_3	$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$	539.2580 ($\text{M}+\text{H}$)	539.2591

TABLE 5A (Cont'd)

Entry

5



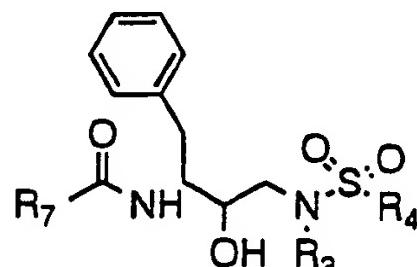
MASS MEASUREMENT

	R^3	R^4	R^7	MOL FORM	CALC (M+H)	FOUND
9				$\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_5\text{S}$	512.2219	512.2271
10				$\text{C}_{28}\text{H}_{35}\text{N}_3\text{O}_5\text{S}$	526.2376	526.2388
11				$\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_5\text{S}$	512.2219	512.2287
12				$\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_5\text{ClS}$	545.1877	545.1887
13				$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$	539.2580	539.2592
14				$\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_5\text{S}$	553.2736	553.2714
15				$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$	539.2580	539.2632
16				$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$	539 (M+H)	539

TABLE 5A (Cont'd)

Entry

5



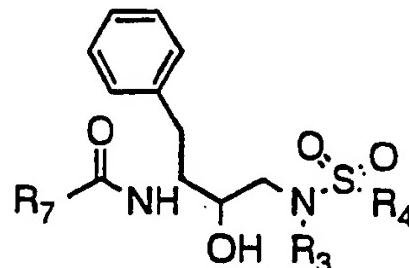
MASS MEASUREMENT

	R ³	R ⁴	R ⁷	MOL FORM	CALC	FOUND
17	CH_2CH_3	$\text{C}_6\text{H}_4\text{OCH}_3$	SO_2CH_3	$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_7\text{S}_2$	589.2042 (M+H)	589.2086
18		$\text{C}_6\text{H}_4\text{SO}_2\text{CH}_3$		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_7\text{S}_2$	595.2124 (M+Li)	595.2103
19		$\text{C}_6\text{H}_4\text{SO}_2\text{CH}_2\text{CH}_3$		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_7\text{S}_2$	595.2124 (M+Li)	595.2191
20			$\text{CH}_2\text{SO}_2\text{CH}_3$	$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_7\text{S}_2$	609.2281 (M+Li)	609.2313
21			$\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$	$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_7\text{S}_2$	603.2199 (M+H)	603.2247
22		$\text{C}_6\text{H}_4\text{SO}_2\text{CH}_2\text{CH}_3$		$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_7\text{S}_2$	603.2199 (M+H)	603.2266

TABLE 5A (Cont'd)

Entry

5

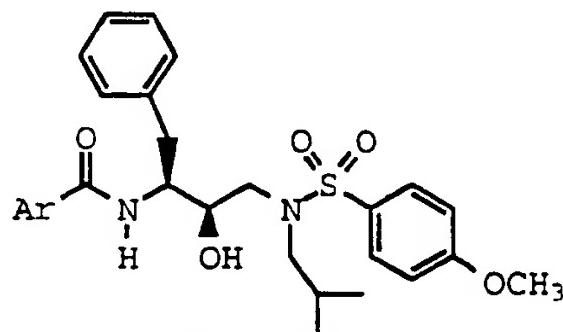


EXACT MASS MEASUREMENT

	R^3	R^4	R^7	MOL FORM	CALC ($\text{M}+\text{H}$)	FOUND
--	--------------	--------------	--------------	----------	---------------------------------	-------

23	$\text{CH}_2\text{CH}_(\text{CH}_3)_2$	C_6H_5	C_6H_5			
24	$\text{CH}_2\text{CH}(\text{CH}_3)_2$	C_6H_5	C_6H_5	$\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$	481.2161	481.2213
25	$\text{CH}_2\text{CH}(\text{CH}_3)_2$	$\text{C}_6\text{H}_5-\text{OCH}_3$	C_6H_5	$\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_5\text{S}$	511.2267	511.2319
26	$\text{CH}_2\text{CH}(\text{CH}_3)_2$	$\text{C}_6\text{H}_5-\text{OCH}_3$	$\text{C}_6\text{H}_5-\text{CH}_3$	$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$	525.2423	525.2469
27			$\text{C}_6\text{H}_5-\text{CH}_3$	$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$	525.2428	525.2464
28		$\text{C}_6\text{H}_5-\text{CH}_3$		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$	525.2423	525.2432
29		$\text{C}_6\text{H}_5-\text{OCH}_3$		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{S}$	541.2372	541.2332
30		$\text{C}_6\text{H}_5-\text{OCO}$		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{S}$	541.2372	541.2355
31		$\text{C}_6\text{H}_5-\text{OCO}$		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{S}$	541.2372	541.2329

TABLE 5B



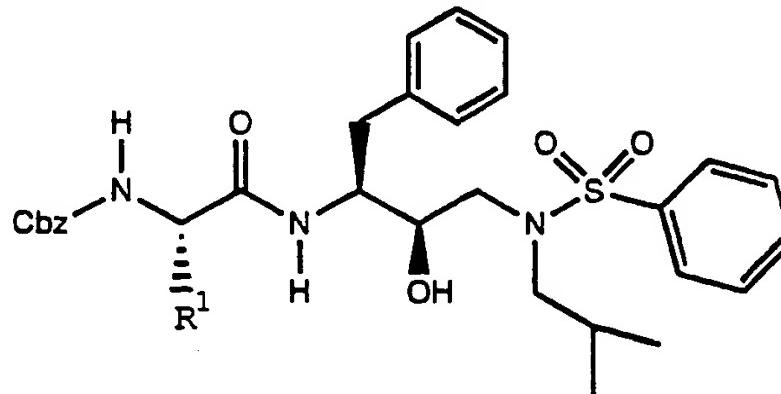
5

<u>Entry</u>	<u>A</u>	<u>Molecular Formula</u>	<u>Mass Spectrum</u>
		C ₂₉ H ₃₅ N ₃ O ₇ S	576 (M+Li)
		C ₂₉ H ₃₇ N ₃ O ₅ S	540 (M+H)
		C ₃₁ H ₄₁ N ₃ O ₅ S	568 (M+H)
		C ₂₉ H ₃₅ N ₃ O ₇ S	570 (M+H)
		C ₂₉ H ₃₇ N ₃ O ₅ S	540 (M+H)

TABLE 5B (contd.)

5

<u>Entry</u>	<u>A</u>	<u>Molecular Formula</u>	<u>Mass Spectrum</u>
		C ₃₁ H ₄₁ N ₃ O ₅ S	568 (M+H)
		C ₂₉ H ₃₅ N ₃ O ₇ S	570 (M+H)
		C ₂₉ H ₃₇ N ₃ O ₅ S	546 (M+Li)
		C ₃₁ H ₄₁ N ₃ O ₅ S	574 (M+Li)

TABLE 6

5

	Entry	R¹
10	1	CH₂SO₂CH₃
	2	(R)-CH(OH)CH₃
	3	CH(CH₃)₂
	4	(R,S)CH₂SOCH₃
	5	CH₂SO₂NH₂
15	6	CH₂SCH₃
	7	CH₂CH(CH₃)₂
	8	CH₂CH₂C(O)NH₂
	9	(S)-CH(OH)CH₃
	10	-CH₂C≡C-H

TABLE 7

5

Entry	R ²	A
10	1 n-Bu	Cbz-Asn
	2 cyclohexylmethyl	Cbz-Asn
	3 n-Bu	Boc
	4 n-Bu	Cbz
	5 C ₆ H ₅ CH ₂	Boc
	6 P-F-C ₆ H ₅ CH ₂	Cbz
15	7 C ₆ H ₅ CH ₂	benzoyl
	8 cyclohexylmethyl	Cbz
	9 n-Bu	Q-Asn
	10 cyclohexylmethyl	Q-Asn
	11 C ₆ H ₅ CH ₂	Cbz-Ile
20	12 C ₆ H ₅ CH ₂	Q-Ile
	13 P-F-C ₆ H ₅ CH ₂	Cbz-t-BuGly
	14 C ₆ H ₅ CH ₂	Q-t-BuGly
	15 C ₆ H ₅ CH ₂	Cbz-Val
	16 C ₆ H ₅ CH ₂	Q-Val
25	17 2-naphthylmethyl	Cbz-Asn
	18 2-naphthylmethyl	Q-Asn
	19 2-naphthylmethyl	Cbz
	20 n-Bu	Cbz-Val
30	21 n-Bu	Q-Val
	22 n-Bu	Q-Ile
	23 n-Bu	Cbz-t-BuGly

TABLE 7 (Cont'd)

Entry	R2	A
5		
24	n-Bu	Q-t-BuGly
25	p-F(C ₆ H ₄)CH ₂	Q-Asn
26	p-F(C ₆ H ₄)CH ₂	Cbz
27	p-F(C ₆ H ₄)CH ₂	Cbz-Asn
10	28 C ₆ H ₅ CH ₂	Cbz-propargylglycine
	29 C ₆ H ₅ CH ₂	Q-propargylglycine
	30 C ₆ H ₅ CH ₂	
		acetylpropargylglycine

TABLE 8

5

Entry	R^3	R^4
10	-CH ₂ CH(CH ₃) ₂	-C(CH ₃) ₂
2	-CH ₂ CH ₂ CH(CH ₃) ₂	
3	-CH ₂ CH ₂ CH(CH ₃) ₂	
4	-CH ₂ CH ₂ CH(CH ₃) ₂	
5	-CH ₂ CH ₂ CH(CH ₃) ₂	

180

TABLE 9

Entry	R	R ¹
1		-CH ₃
10		-CH ₃
2		-CH ₃
3		-CH(CH ₃) ₂
4		-CH(CH ₃) ₂
5		-C(CH ₃) ₃
6		-CH ₃
15		-CH ₃
7		

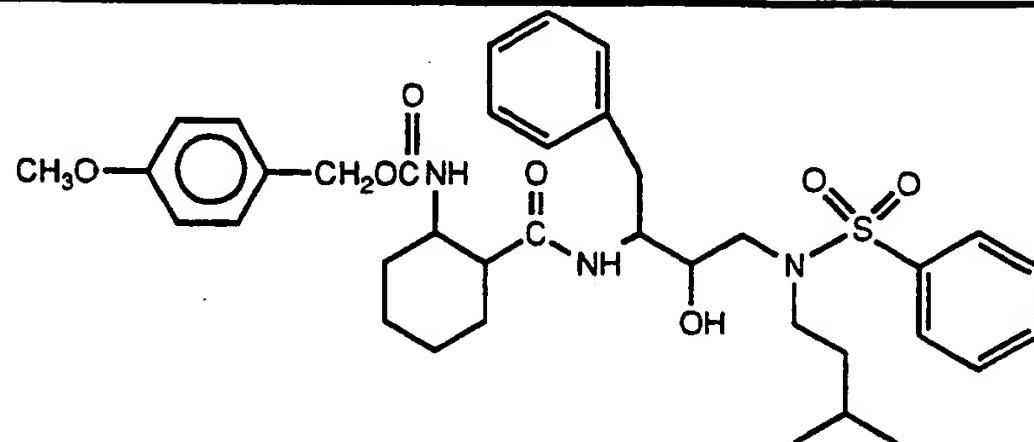
Table 9 (Cont'd)

5	Entry	R	R ¹
8		$\text{HO}_2\text{CCH}_2\text{CH}_2-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$	-CH ₃
9			-CH ₃
10	10	$\text{CH}_3\text{NH}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$	-CH ₃
11		$(\text{CH}_3)_2\text{CH}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$	-CH ₃
15	12	$\text{CH}_3\text{OCH}_2-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$	-CH ₃
	13	$(\text{CH}_3)_2\text{NCH}_2-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$	-CH ₃
	14	$\text{CH}_3\text{CH}(\text{OH})-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$	-CH ₃

TABLE 9 (Cont'd)

5 Entry

15



16

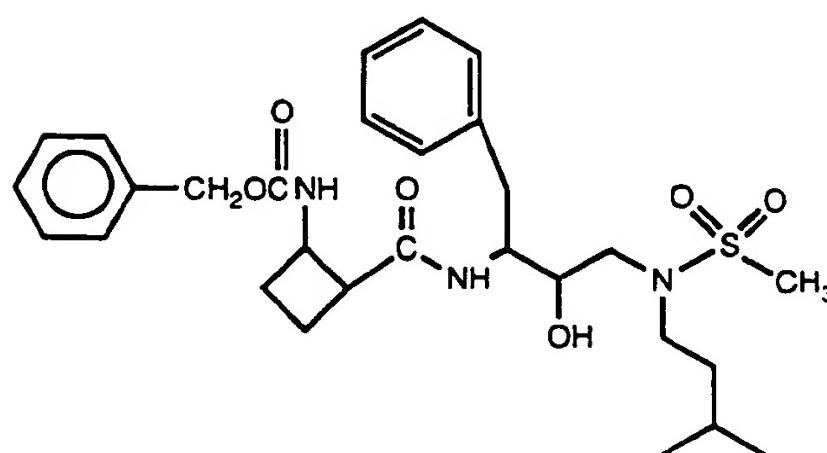


TABLE 10

5

Entry	R ¹	R ^{1'}	R ^{1''}	R
1	H	H	H	
10	2	H	H	
3	H	CH ₃	H	
4	H	CH ₃	CH ₃	
5	H	H	CO ₂ CH ₃	
15	6	H	H	
7	H	H	H	
8	H	H	CONH ₂	Cbz
9	H	H	CONH ₂	2-quinolinylcarbonyl

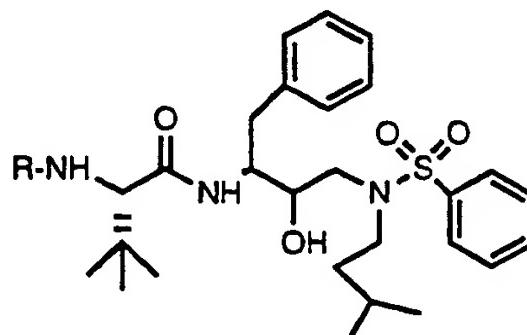
TABLE 11

5

Entry	R	R'	X
10	1 R=H	R'=H	X=H
	2 R=Me	R'=Me	X=H
	3 R=H	R'=Me	X=H
	4 R=Me	R'=Me	X=F
	5 R=H	R'=Me	X=F
15	6 R=Cbz	R'=Me	X=H
	7 R=H	R'=Bz	X=H
	8 R+R'=pyrrole	X=H	

20

TABLE 12



	Entry	Acyl Group (R)
10	1	benzyloxycarbonyl
	2	<u>tert</u> -butoxycarbonyl
	3	acetyl
	4	2-quinoylcarbonyl
	5	phenoxyacetyl
	6	benzoyl
15	7	methyloxaloyl
	8	pivaloyl
	9	trifluoracetyl
	10	bromoacetyl
20	11	hydroxyacetyl
	12	morpholinylacetyl
	13	N,N-dimethylaminoacetyl
	14	N-benzylaminoacetyl
	15	N-phenylaminoacetyl
25	16	N-benzyl-N-methylaminoacetyl
	17	N-methyl-N-(2-hydroxyethyl)aminoacetyl
	18	N-methylcarbamoyl
	19	3-methylbutyryl
	20	N-isobutylcarbamoyl
	21	succinoyl (3-carboxypropionyl)
30	22	carbamoyl
	23	N-(2-indanyl)aminoacetyl

TABLE 13

5

Entry	R^3	R^4
10	1 -CH ₃	-n-Butyl
	2 -i-Butyl	-CH ₃
	3 -i-Butyl	-n-Butyl
	4 -i-Propyl	-n-Butyl
	5 -C ₆ H ₅	-n-Butyl
15	6 -CH ₂ -	-n-Butyl
	7 -CH ₂ -	-n-Butyl
	8	-n-Butyl
	9 -i-Butyl	-n-Propyl
	10 -i-Butyl	-CH ₂ CH(CH ₃) ₂
20	11 -(R)-CH(CH ₃)-	-n-Butyl
	12 -CH ₂ -	-i-Propyl
	13 -CH ₂ -	-CH ₂ CH ₂ CH(CH ₃) ₂
	14 i-Butyl	-CH ₂ CH ₃
	15 i-Butyl	-CH(CH ₃) ₂
	16 i-Butyl	

TABLE 13 (cont.)

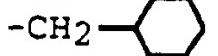
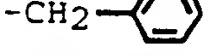
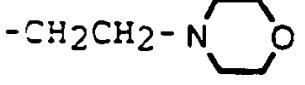
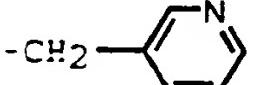
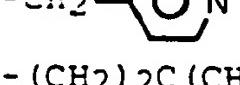
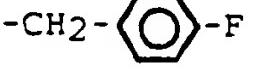
Entry	R ³	R ⁴
5		
17	-CH ₂ - 	- (CH ₂) ₂ CH(CH ₃) ₂
18	(CH ₂) ₂ CH(CH ₃) ₂	-CH(CH ₃) ₂
19	i-Butyl	-CH(CH ₃) ₂
20	i-Butyl	-C(CH ₃) ₃
10	21 -CH ₂ - 	-C(CH ₃) ₃
	22 - (CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃
	23 -CH ₂ C ₆ H ₅	-C(CH ₃) ₃
	24 - (CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃
	25 n-Butyl	-C(CH ₃) ₃
15	26 n-Pentyl	-C(CH ₃) ₃
	27 n-Hexyl	-C(CH ₃) ₃
	28 -CH ₂ - 	-C(CH ₃) ₃
	29 -CH ₂ C(CH ₃) ₃	-C(CH ₃) ₃
	30 -CH ₂ CH ₂ -N 	-C(CH ₃) ₃
20	31 -CH ₂ C ₆ H ₅ OCH ₃ (para)	-C(CH ₃) ₃
	32 -CH ₂ - 	-C(CH ₃) ₃
	33 -CH ₂ - 	-C(CH ₃) ₃
	34 - (CH ₂) ₂ C(CH ₃) ₃	-C(CH ₃) ₃
	35 - (CH ₂) ₄ OH	-C(CH ₃) ₃
25	36 -CH ₂ - 	-C(CH ₃) ₃

TABLE 13 (cont.)

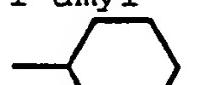
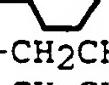
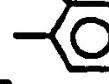
Entry	R ³	R ⁴
5		
37	-CH ₂ - 	-C(CH ₃) ₃
38	-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
39	i-amyl	-CH ₂ C(CH ₃) ₃
		
40		-CH ₂ C(CH ₃) ₃
		
10		
41		-CH ₂ C(CH ₃) ₃
42	i-butyl	-CH ₂ C(CH ₃) ₃
43	-CH ₂ Ph	-Ph
44	-CH ₂ - 	-Ph
45	-CH ₂ - 	-Ph
15		
46	-CH ₂ - 	-Ph
47	-CH ₂ - 	-Ph
48	-CH ₂ - 	-Ph
49	-CH ₂ CH=CH ₂	-Ph
50	- 	-Ph
20		
51		-Ph
52	-CH ₂ CH ₂ Ph	-Ph
53	-CH ₂ CH ₂ CH ₂ CH ₂ OH	-Ph
54	-CH ₂ CH ₂ N(CH ₃) ₂	-Ph
55	-CH ₂ CH ₂ -N 	-Ph
25		
56	-CH ₃	-Ph

TABLE 13 (cont.)

Entry	R^3	R^4
5	57 -CH ₂ CH ₂ CH ₂ SCH ₃	-Ph
	58 -CH ₂ CH ₂ CH ₂ S(O) ₂ CH ₃	-Ph
	59 -CH ₂ CH ₂ CH(CH ₃) ₂	- 
10	60 -CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ - 
	61 -CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ CH ₂ CH ₃
	62 -CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₃
	63 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -F
15	64 -CH ₂ CH ₂ CH(CH ₃) ₂	- 
	65 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -NO ₂
	66 -CH ₂ CH ₂ CH(CH ₃) ₂	- 
20	67 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -OCH ₃
	68 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -NO ₂
	69 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -CF ₃
	70 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -NHAc
20	71 -CH ₂ CH ₂ CH(CH ₃) ₂	-  -Cl
	72 -CH ₂ CH ₂ CH(CH ₃) ₂	

TABLE 13 (cont.)

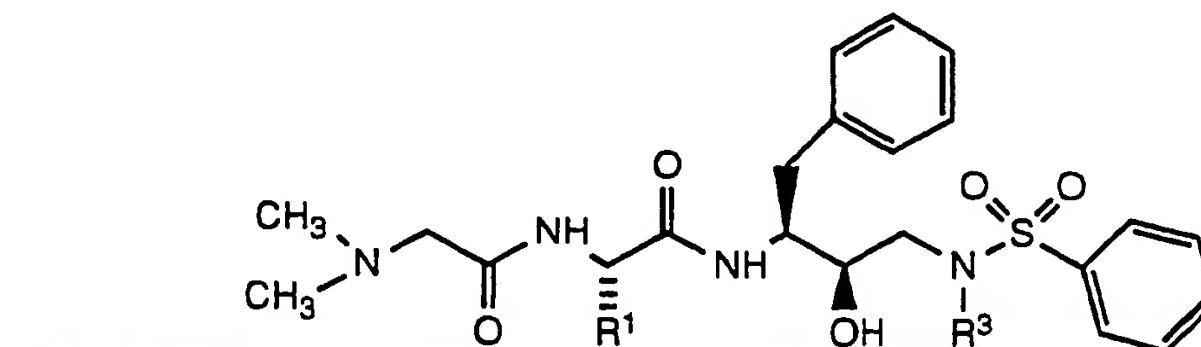
Entry	R ³	R ⁴
5		
73	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -CH ₃
74	-CH ₂ CH ₂ CH(CH ₃) ₂	CO ₂ CH ₃ - 
75	-CH ₂ CH(CH ₃) ₂	- 
76	-CH ₂ CH(CH ₃) ₂	-  -F
10	77	-CH ₂ CH(CH ₃) ₂
	78	-CH ₂ CH(CH ₃) ₂
	79	-CH ₂ CH ₂ CH ₃
	80	-CH ₂ CH ₂ CH ₂ CH ₃

15

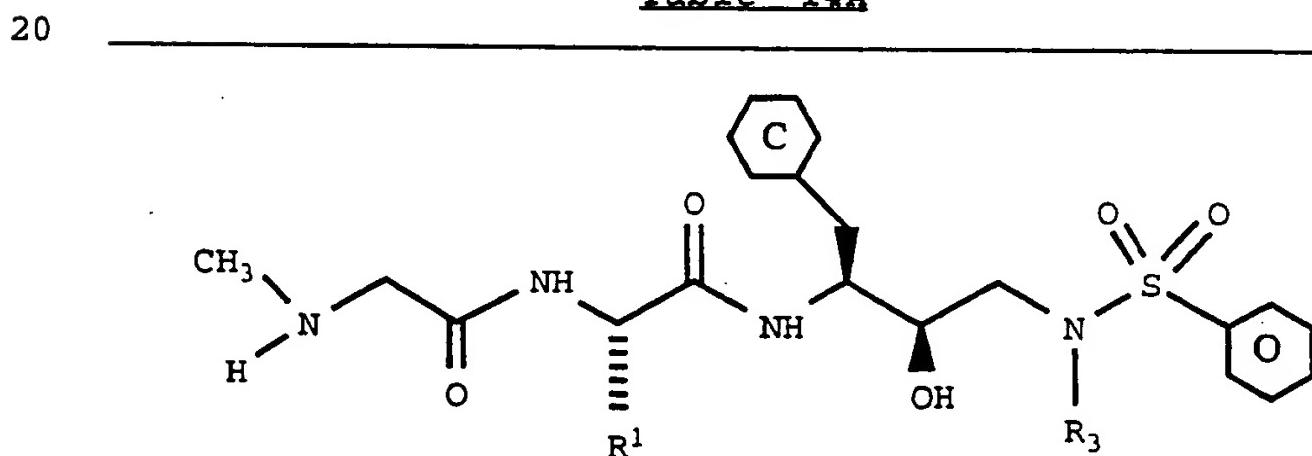
a benzyloxycarbonyl
 b 2-quinolinylcarbonyl

20

191

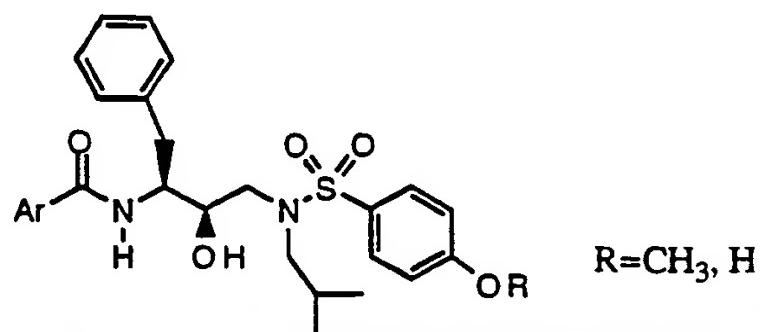
Table 14

	Entry	R ¹	R ³
10	1	C(CH ₃) ₃	CH ₂ CH ₂ CH(CH ₃) ₂
	2	CH ₂ C≡CH	CH ₂ CH ₂ CH(CH ₃) ₂
	3	C(CH ₃) ₂ (SCH ₃)	CH ₂ CH ₂ CH(CH ₃) ₂
	4	C(CH ₃) ₂ (S[O]CH ₃)	CH ₂ CH ₂ CH(CH ₃) ₂
	5	C(CH ₃) ₂ (S[O] ₂ CH ₃)	CH ₂ CH ₂ CH(CH ₃) ₂
15	6	C(CH ₃) ₃	CH ₂ CH(CH ₃) ₂
	7	C(CH ₃) ₃	cyclohexyl
	8	CH(CH ₃) ₂	CH ₂ CH(CH ₃) ₂
	9	CH(CH ₂ CH ₃)(CH ₃)	CH ₂ CH(CH ₃) ₂

Table 14A

Entry	R ¹	R ³
1	C(CH ₃)SCH ₃	CH ₂ CH ₂ CH(CH ₃) ₂

Table 15



5

A.F.

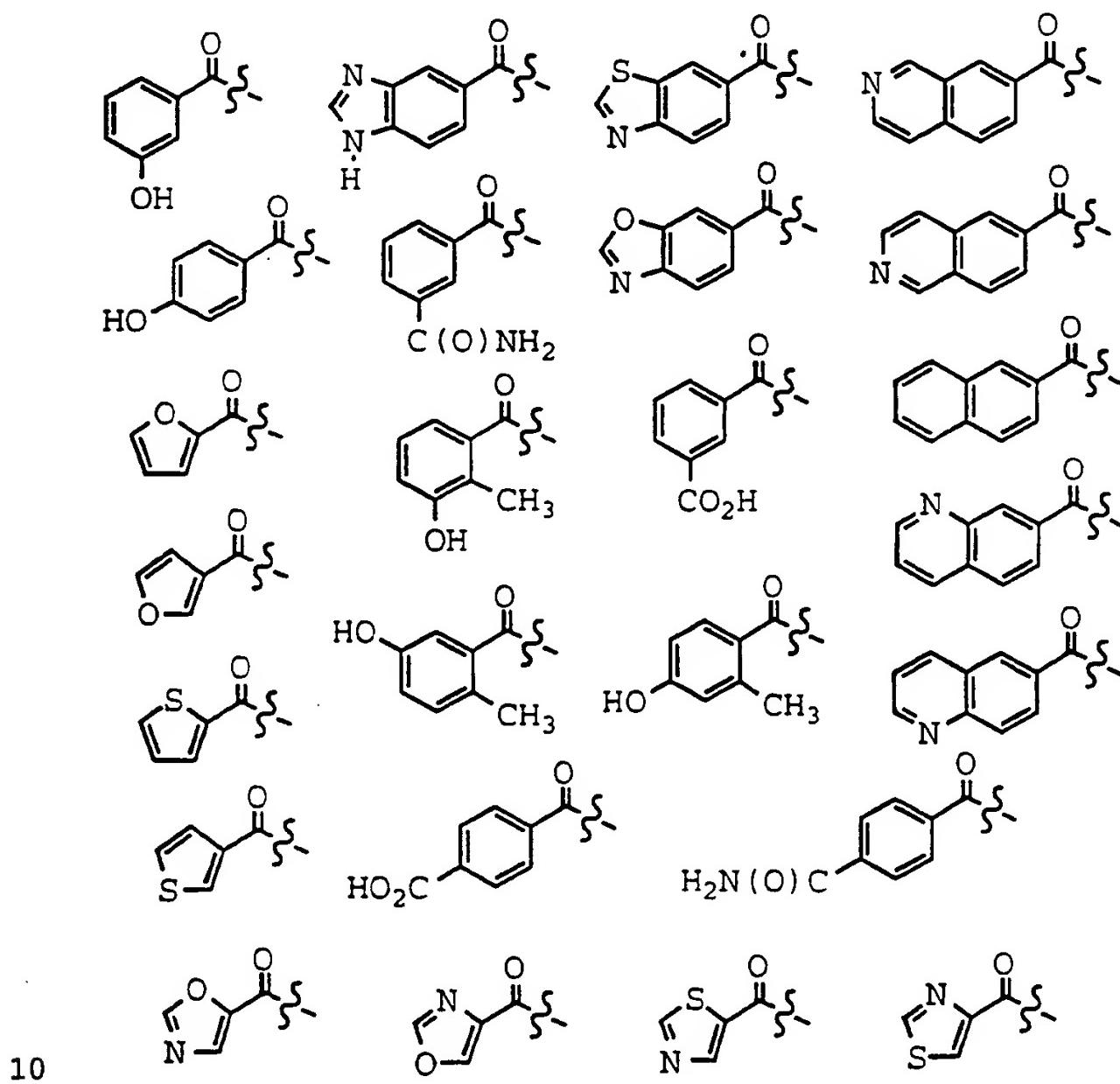
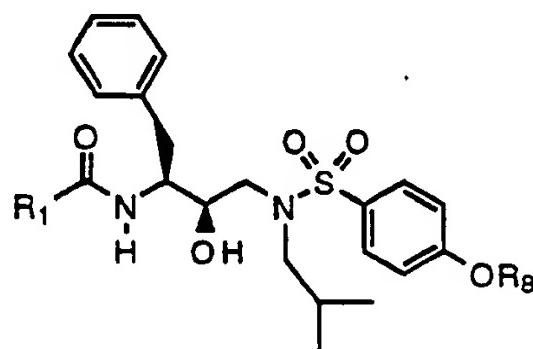


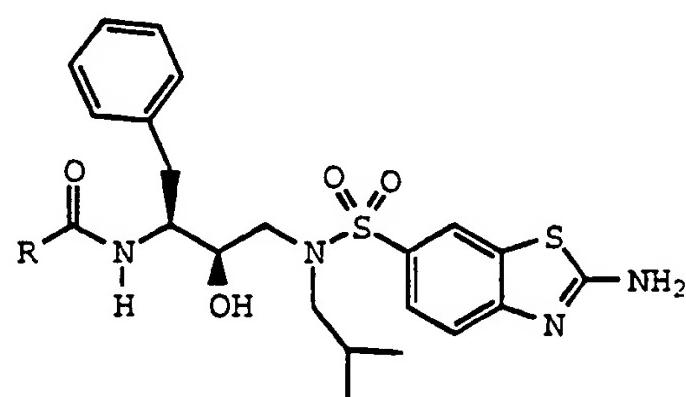
Table 16



5

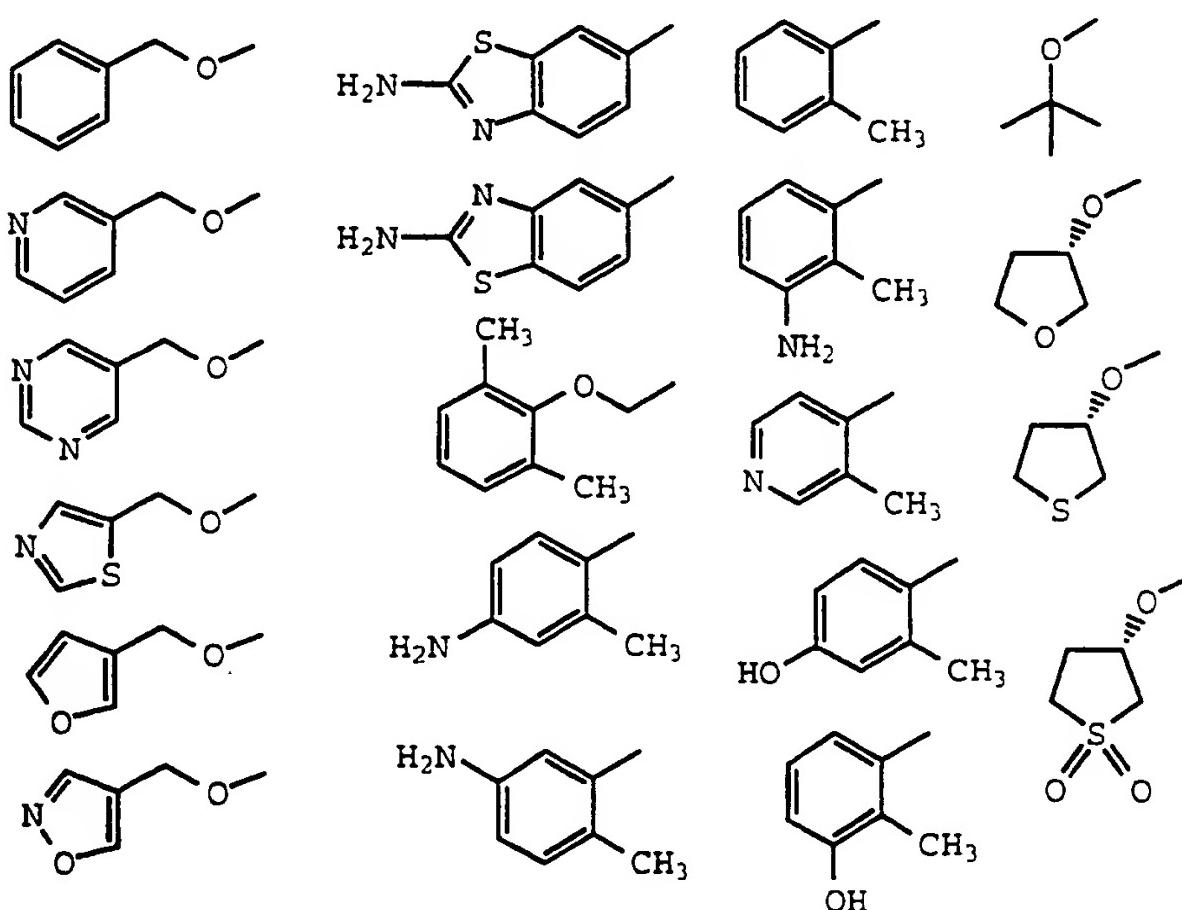
R₁	R₈	R₁	R₈
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃		H or CH ₃
	H or CH ₃	<img alt="Chemical structure of 2-(2-methylpyridin-4-yl)pyridine-4-ylmethyl piperidin-4-ylmethyl morpholine-4-ylmethyl piperidine-4-ylmethyl morpholine-4-ylmethyl morpholine-4-ylmethyl morpholine-4	

Table 16A



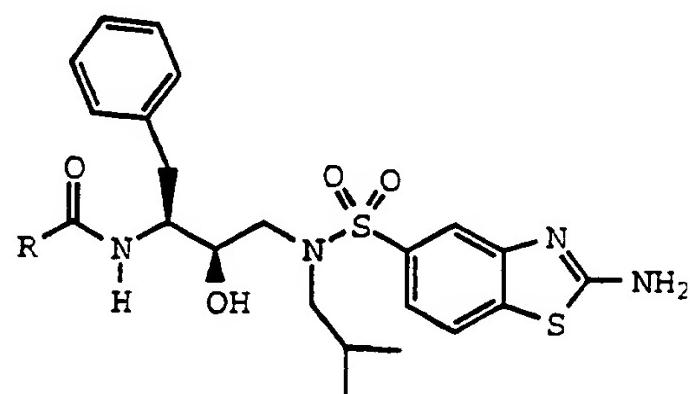
5

R



10

Table 16B



5

R

10

